ISSN 2704-3045

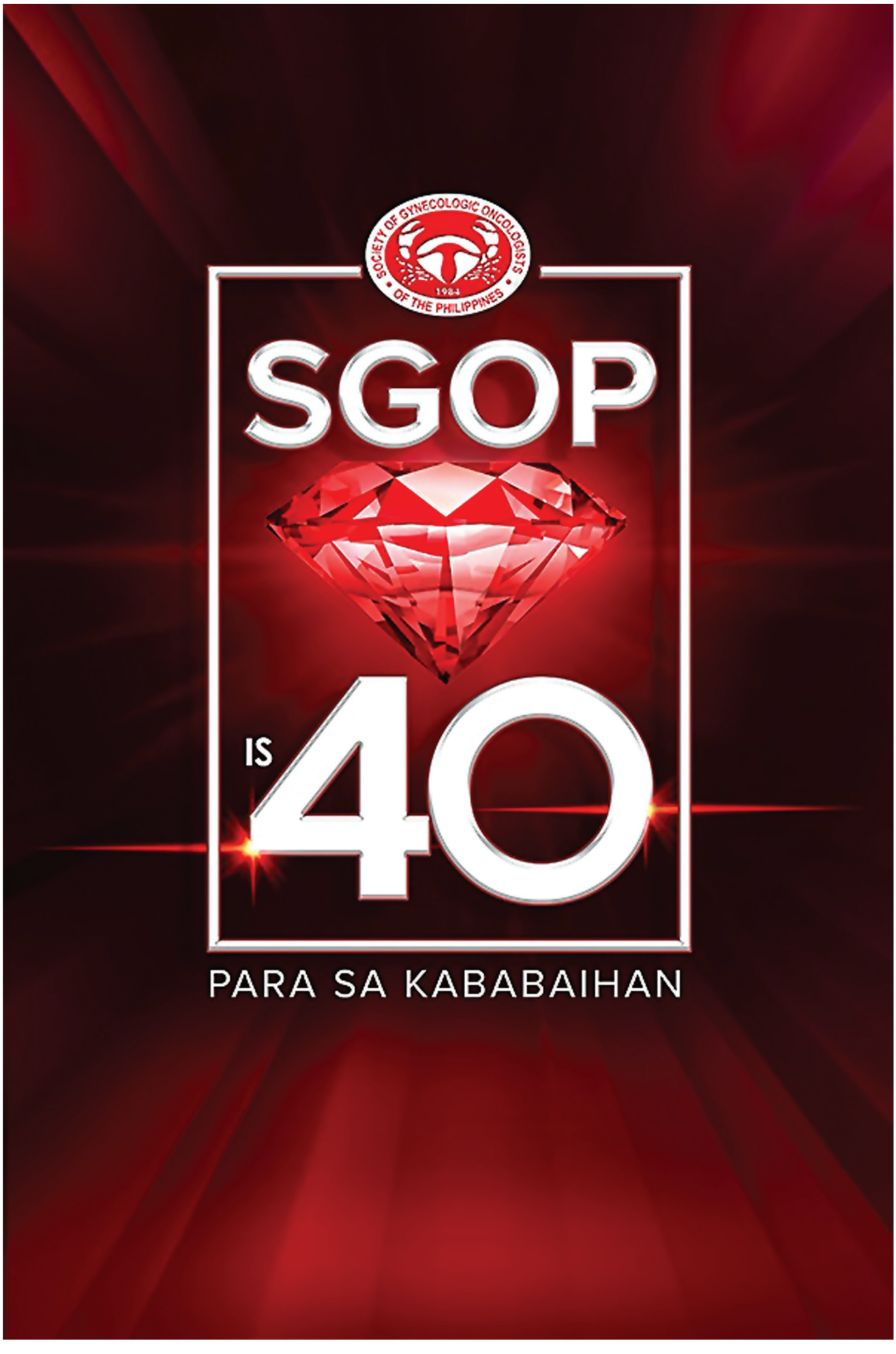
The Philippine Journal of GYNECOLOGIC ONCOLOGY

Official Publication of the Society of Gynecologic Oncologists of the Philippines

Volume 19 Number 1 June 2024

ORIGINAL PAPERS

CASE REPORTS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Offcial Publication of the Society of Gynecologic Oncologists of the Philippines

Volume 19 Number 1 June 2024

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Official Publication of the Society of Gynecologic Oncologists of the Philippines

Volume 19 Number 1 June 2024

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The Philippine Journal of Gynecologic Oncology (ISSN 2704-3045) is the peer-reviewed journal produced as a program of the Society of Gynecologic Oncologists of the Philippines (SGOP). It is published biannually by the SGOP with business and production offices at Unit 404, Manila Astral Towers, 1330 Taft Ave. cor. Padre Faura Sts., Ermita, Manila, Philippines.

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The Philippine Journal of Gynecologic Oncology (PJGO) is the official publication of the Society of Gynecologic Oncologists of the Philippines, Inc. (SGOP). It is a peer-reviewed journal that covers all aspects in gynecologic oncology and features original research papers and case reports, as well as correspondences. The journal is published biannually and sent by courier mail to all SGOP members in good standing, all POGS-accredited training institutions and medical schools.

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BOOK

Cunningham FG, Gant NF, Leveno KJ, Gilstrap III LC, Hauth JC and Wenstrom KD (eds): Williams Obstetrics, 21st ed. USA: McGraw-Hiall, 2001.

CHAPTER IN BOOK

Mishell DR. Amenorrhea. In: Droegemuller W, Herst AL, Mishell DR, Stencheber MA (eds): Comprehensive Gynecology. St. Louis: CV Mosby Co., 1987: 15.

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Knowledge and Practices on Cervical Cancer Screening among Philippine Obstetrical and Gynecological Society (POGS) – accredited Obstetricians and Gynecologists Practitioners in Philippine Hospitals Obstetricians and Gynecologists Practitioners in Philippine Hospitals

Bernadette C. Yap, MD and Jean Anne B. Toral, MD, MSc, FPOGS, FSGOP, FPSCPC

ABSTRACT

Background: Cervical cancer is a very deadly disease afflicting Filipino women. Screening is the most effective secondary prevention for cervical cancer. Effective screening continues to decrease the incidence of cases and deaths from cervical cancer. Proper understanding and explanation of the attending physician to the patients are essential as the women often do not experience symptoms until the disease has advanced.

Objective: This study aims to determine the knowledge and practices on cervical cancer screening among Philippine Obstetrical and Gynecological Society – accredited obstetricians and gynecologists practitioners in the country.

Methodology: A cross sectional survey was conducted among POGS-accredited (diplomates and fellows) practitioners in the whole country. The survey questionnaire and informed consent forms were disseminated via Google forms. Differences between the knowledge and practices regarding cervical cancer screening among obstetrics and gynecology practitioners based on years in practice, attendance in continuing medical education (CME) activities, location of practice, and hospital affiliation were determined.

Results: A total of 211 obstetricians and gynecologists practitioners from 26 hospitals responded in the survey. The perceived effectiveness of cervical cancer screening by the participants differed significantly by years of practice for Pap test by conventional cytology (p-value=0.040) and Pap test by liquid-based cytology (e.g. Thin Prep or SurePath®) (p-value=0.010). In both two types of screening method, those with less than 5 years of practice had the highest proportion who reported that these were very effective (54.2% and 72.9%, respectively). It also differed significantly by location of practice for HPV DNA test with Pap test (p-value=0.000). The same goes for hospital type for HPV DNA test with Pap test (p-value=0.026). Those with less than 5 years of practice significantly had the highest mean number of responses (6.2±2.0) consistent with guidelines on frequency of Pap smear (p-value<0.001). The mean number of responses consistent with the guidelines in frequency of Pap smear in 10 different cases was 5.5±1.9. The rates of responses consistent with the guidelines in frequency of Pap smear varied from 25.6% to 92.9%. The mean number of responses consistent with the guidelines in Pap smear test with HPV DNA testing and HPV vaccine in 4 different cases was 2.5±0.5. The rates of responses consistent with the guidelines in Pap smear test with HPV DNA testing and HPV Vaccine varied from 24.1% to 90.1%. Also, HPV DNA testing was routinely performed by 58.8% of the participants only. The practice of referring abnormal Pap smear findings with HPV DNA test positive also varied greatly among the participants (46.5%-67.3%).

Conclusions: Obstetricians and gynecologists practitioners have average knowledge of current cervical cancer screening guidelines. Years in practice, location of practice, and type of institution affiliated to are significant factors that may affect knowledge and practice on cervical cancer screening. Further studies are recommended to explore additional factors which causes variation in practice of cervical cancer screening in the country.

Keywords: Cervical cancer, Cervical cancer screening, Pap test

INTRODUCTION

Cervical cancer screening recommendations has evolved throughout the years into the current, effective algorithms for screening and management. The addition of human papillomavirus testing and genotyping has allowed for more efficient, effective and less invasive management of cervical cancer screening[1]. There are proven advantages of the new guidelines; however, there are barriers in applying them into practice.

The American Society for Colposcopy and Cervical Pathology (ASCCP), among other organizations, released amended

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3rd Place, SGOP 2021 Research Paper Contest in Gynecologic Oncology, 19 November 2021 via Zoom webinar platform

Financial Disclosure:
The authors did not report any potential conflicts of interest.

guidelines that allowed for the option of human papillomavirus (HPV) genotyping alone or in tandem with Pap smear for routine screening in certain populations.

Many countries, mostly developed and first-world, around the world have already fully implemented the utilization of primary HPV testing to screen the population either for all patients or for certain populations based on age and location. Evidence shows that the HPV tests are sensitive and effective in identifying women at risk for developing precancerous lesions.[2]

The changes in the new guidelines were significant. The guidelines allowed for fewer but targeted screening for women, without increased in incidence of advanced stage cervical cancer. This will allow less healthcare expenditures and decreased unnecessary screening.[3] Practicing physicians may or may not be familiar with the new released guideline or may not believe in its effectivity.

This research assessed the knowledge and practices of Philippine Obstetrical and Gynecological Society (POGS) – accredited obstetricians and gynecologists practitioners in Philippine hospitals in relation to the cervical cancer screening at the national level. This study provides baseline information in terms of the practice of cervical cancer screening in the country. The country is at risk of increase in the incidence of cervical cancer due to the lack of a structured screening program. The role of healthcare providers spearheaded by obstetrician-gynecologists is of utmost importance. Knowing their knowledge and their practices on this important health elated matter will help direct continuing education programs to this end all in the effort to better the healthcare delivery for women in the fight against cervical cancer.

MATERIALS AND METHODS

Study Design, Population, and Sample Size

A cross-sectional study was conducted among Philippine Obstetrical and Gynecological Society (POGS) – accredited Obstetricians and Gynecologists practitioners in Philippine hospitals. The study population included Philippine Obstetrics and Gynecology Society (POGS) - accredited fellows and diplomates in active practice, with informed consent and valid active electronic email addresses.

To ensure appropriate and equal representation from each group of healthcare professionals, randomized sampling was utilized. A list of hospitals accredited for training and/or service were obtained from the POGS. Multi-stage stratified cluster sampling was used in determining the hospitals whose practitioners will be asked to participate in the study. The regions served as strata which had equal proportions of hospitals to be included in the study based on whether the hospital is private or government-owned. The hospitals served as clusters and were randomly picked through computer lottery using the online randomizer https://www.randomizer.org/. All practitioners from the selected hospitals were included in the study.

Using a frequency of 50% to achieve the highest possible sample size, +/-7.5% margin of error, 5% level of significance, and 10% adjustment for drop-outs, this study needed a minimum of 182 respondents in order to represent the total population of obstetrician-gynecologist practitioners.

Operational Definition of Terms

1. Primary prevention- aims to prevent disease or injury before it ever occurs. This is done by preventing exposures to hazards that cause disease or injury, altering unhealthy or unsafe behaviors that can lead to disease or injury, and increasing resistance to disease or injury should exposure occur. For cervical cancer, this is through HPV vaccination.
2. Secondary prevention- emphasizes early disease detection and its target is healthy appearing individuals with subclinical forms of the disease. Subclinical disease consists of pathologic changes, but no overt symptoms that are diagnosable in screening tests. For cervical cancer, this is through screening for premalignant diseases.
3. Papanicolaou (Pap) testing - developed in the 1940s by Georgios Papanikolaou. It involves exfoliating cells from the transformation zone of the cervix to enable examination of these cells microscopically for detection of cancerous or precancerous lesions.
4. Conventional Pap slide “smear” - involves direct transfer of the cervical cells to a microscope slide for evaluation. This traditional method may introduce confounders such as blood and other debris to the slide, which may make interpretation more difficult.
5. Liquid-based cytology - collected cells are released into a vial of liquid preservative that is then used in the cytology lab to produce a slide for microscopic evaluation of the cells
6. Ayre’s spatula - a wooden device used to collect Pap smear. It is a spatula with a U-shaped opening on one side and a flat surface on another
7. Cotton pledget – a stick with compress or small flat mass usually of gauze or absorbent cotton that is usually used for smears
8. Cytobrush - A long cotton swab with a conical head used to collect endocervical cell samples
9. Human papilloma virus (HPV) - represents a family of double-stranded, circular DNA viruses that can infect skin or mucosal cells, including the anogenital region and the oral cavity, and may be transmitted easily via sexual intercourse or direct contact
10. Precursor lesions – squamous intraepithelial lesions (SIL) are graded 1–3 according to the degree of epithelial atypia. Low-grade SIL (1/2) mainly result from a productive HPV infection and are likely to regress after virus clearance. High-grade SIL harbor a HPV infection and can develop within 3 years after a persistent high-risk HPV infection. Progression to cervical cancer might take another 10–30 years
11. Borderline cytology lesions- mild dyskaryosis, cytological abnormalities which is the same as atypical squamous cells of undetermined significance (ASCUS)
12. Human papillomavirus (HPV) DNA test- A laboratory test in which cells are scraped from the cervix to look for DNA of human papillomaviruses (HPV). Test results are reported as:
    a. Positive test (High-risk)- a type of high-risk HPV DNA is detected in the test (i.e., 16, 18)
    b. Positive test (High-risk)- a type of high-risk HPV DNA is detected in the test (i.e., 45)
    c. Positive test (Others)- a type of high-risk HPV DNA is detected in the test (i.e., Other types than 16, 18, 45)

d. Negative test- no high-risk HPV DNA that causes cancer

13. POGS fellow - a member who has been board certified in the practice of Obstetrics and Gynecology after being a diplomate for at least 2 years and fulfilled the requirements set by the POGS.
14. POGS diplomate- a member who has passed both written and oral examinations given by the Philippine Board of Obstetrics and Gynecology.

Description of Study Procedures, Data Collection Tools and Analysis

Data were collected through a self-administered questionnaire. The electronic questionnaire was rendered available via Google Forms which was made accessible via a link sent to their emails. This method was deemed convenient for the participants especially for those who are in the difficult to reach places. There was an informed consent made available via Google Forms. The researcher sent a detailed message regarding the informed consent. If there were any questions or clarifications, the researcher will call the participant with the registered mobile number.

The questionnaire was set up in a way that the participant needs to click on a "button" or on a response to signify that he/she agrees to participate. The questionnaire used in this study was adopted from the form used in a national study done in USA by their National Cancer Institute. The survey was designed by an academic physician and validated by an expert panel consisting of epidemiologists, public health specialists, family physicians, microbiologists and academic professionals. The survey was pilot tested by 20 physicians for face validity and comprehensibility. The author gave permission to the researcher that the questionnaire be used for the purpose of this study.

The questionnaire was pilot tested among 10 OB GYNE consultants in the country. Cognitive debriefing was made after every respondent finished the questionnaire. Recommendations were given on how the survey can be improved. The questionnaire consisted of: 1) Items regarding the respondents' demographic data 2) Items on beliefs of effectivity of screening procedures in reducing cervical cancer mortality 3) Practice of performing Pap smear in different situations, 4) Screening practices in the clinic, 5) HPV DNA test usage, and 6) Recommendation of interval of Pap Smear.

A letter explaining the research was sent by electronic mail to the participants included in the cluster sampling. The questionnaire and informed consents were disseminated through Google Forms. The primary researcher collected the questionnaires via the reply in the electronic mail. All data gathered from the respondents were treated as confidential information.

The data were extracted by the investigator from the questionnaires in Google Forms. These are directly linked to an electronic spreadsheet, accessed only by the principal investigator. Subsequent data processing and analysis was carried out using the software Stata 13.

Descriptive statistics such as mean and standard deviation were used to describe age in years and duration of clinical practice; while frequency and percentage were used to describe their practice if private or service, the place of practice, and the region of the hospital. For questions with categorical responses, the proportion of responses were presented using actual frequency and percentage. Current practices of obstetrician-gynecologists on cervical cancer screening methods were summarized using frequencies and proportion of responses to questions 1,2,3,4,8,9 and 10. Current application HPV typing and testing in the practice were summarized using frequencies and proportion of responses to question 6b. Knowledge were summarized using frequencies and proportion of responses to questions 5, 6a, and 7. The current guidelines used for cervical cancer screening are based on the 2020 American Cancer Society (ACS) Guidelines for the prevention of cervical cancer[4] and the 2019 ASCCP Risk Based Management Consensus Guidelines[5]. Chi-square test was used to compare the proportion of responses in each question among practitioners in terms of years in practice, attendance in Continuing Medical Education (CME) activities, location of practice (urban and rural), and private and government hospitals. SPSS 23 was used for analysis. The level of significance for all sets of analysis was set at a pvalue less than 0.05 using two-tailed comparisons.

RESULTS

A total of 211 obstetricians and gynecologists practitioners from 26 hospitals responded to the survey. Table 1 shows the baseline demographics of all the respondents in the survey. Their mean age was 45±9.9 years old. Almost half of the hospitals were private (45.5%) and majority came from regions outside NCR (79.6%). Majority were married (70.1%) and the mean length of practice was 12.9±10.8 years. Majority of the participants were General OBGYN (55.5%). In terms of attendance to CME activities, majority attended more than 5 per year (64.0%).

Table 1. Baseline demographics for participants of the study (n,%)

	N=21
Age	45±9.9
Type of hospital	
Government	115 (54.5)
Private	96 (45.5)
Region of hospital	
NCR	43 (20.4)
Others	168 (79.6)
Civil Status	
Single	60 (28.4)
Married	148 (70.1)
Others	3 (1.5%)
Years in Practice	12.9±10.8
Subspecialty	
General OBGYN	117 (55.5)
Family Planning	1 (0.5)
Gynecologic Oncology	16 (17.6)
Perinatology	11 (5.2)
Reproductive Endocrinology	15 (17.1)
Trophoblastic diseases	3 (1.4)
Ultrasound	27 (12.8)
Minimally Invasive Surgery	10 (4.7)
Maternal Fetal Medicine	8 (3.8)
OB- Infectious Diseases	2 (1.0)
Attendance to continuing medical education (CME) activities	
0/ year	2 (1.0)
1-2/ year	12 (5.7)
3-4/year	62 (29.4)
>5/year	135 (64.0)

In terms of effectivity of cervical cancer screening methods, HPV DNA test with Pap test (82.9%) were reported to be very effective by most of the participants followed by Pap test (liquid based cytology e.g., Thin Prep or SurePath®) (62.6%) (Table 2). Table 2a shows the effectivity of different types of screening stratified by years of practice. The perceived effectiveness of the screening methods by the participants differed significantly by years of practice for Pap test (conventional cytology) (p-value=0.040) and Pap test (liquid based cytology) (p-value=0.010). In both types of screening methods, those with less than 5 years of practice had the highest proportion who reported that these were very effective (54.2% for Pap and 72.9% for liquid-based, respectively). The perceived effectiveness by the participants did not differ significantly by attendance to CME activities (Table 2b).

Table 2. Knowledge – Effectivity of different types of screening (n,%)

	Very Effective	Somewhat Effective	Not Effective	Effectiveness Not Known	Not Sure
a. Pap test (conventional cytology)	71 (33.6)	136 (64.5)	3 (1.4)	1 (0.5)	0 (0.0)
b. Pap test (liquid based cytology e.g., Thin Prep or SurePath®)	132 (62.6)	72 (34.1)	3 (1.4)	4 (1.9)	0 (0.0)
c. HPV DNA test with Pap test	175 (82.9	26 (12.3)	1 (0.5)	6 (2.8)	3 (1.4)
d. VIA (Visual inspection with acetic acid)	48 (22.8)	157 (74.4)	0 (0.0)	5 (2.4)	1 (0.5)
e. VILI (Visual inspection with Lugol's iodine)	48 (22.8)	136 (64.5)	5 (2.4)	8 (3.8)	14 (6.6)

Table 2a. Knowledge – Effectivity of different types of screening, by years of practice (n,%)

	Very Effective	Somewhat Effective	Not Effective	Effectiveness Not Known	Not Sure	p-value
a. Pap test (conventional cytology)						
<5 year	32 (54.2)	33 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.040
5 to 10 years	21 (28.2)	33 (60.0)	1 (1.8)	0 (0.0)	0 (0.0)	
>10 years	23 (23.7)	71 (73.2)	2 (2.1)	1 (1.0)	0 (0.0)	
b. Pap test (liquid-based cytology e.g., Thin Prep or SurePath®)						
<5 year	43 (72.9)	15 (25.4)	0 (0.0)	0 (0.0)	1 (1.7)	0.010
5 to 10 years	38 (69.1)	15 (27.3)	0 (0.0)	0 (0.0)	2 (3.6)	
>10 years	51 (52.6)	42 (43.3)	0 (0.0)	4 (4.1)	0 (0.0)	
c. HPV DNA test with Pap test						
<5 year	48 (81.4)	11 (18.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.053
5 to 10 years	46 (83.6)	6 (10.9)	1 (1.8)	0 (0.0)	2 (3.6)	
>10 years	81 (83.5)	9 (9.3)	0 (0.0)	6 (6.2)	1 (1.0)	
d. VIA (Visual inspection with acetic acid)						
<5 year	10 (16.9)	46 (78.0)	0 (0.0)	3 (5.1)	0 (0.0)	0.455
5 to 10 years	13 (23.6)	42 (76.4)	0 (0.0)	0 (0.0)	1 (1.0)	
>10 years	25 (25.8)	69 (71.1)	0 (0.0)	2 (2.1)	1 (1.0)	
e. VILI (Visual inspection with Lugol's iodine)						
<5 year	13 (22.0)	41 (69.5)	0 (0.0)	4 (6.8)	1 (1.7)	0.268
5 to 10 years	13 (23.6)	36 (65.5)	1 (1.8)	0 (0.0)	5 (9.1)	
>10 years	22 (22.7)	59 (60.8) 4	4 (1.2)	4 (4.1)	8 (8.3)	

Table 2b. Knowledge – Effectivity of different types of screening, by attendance to CME activities (n,%)

	Very Effective	Somewhat Effective	Not Effective	Effectiveness Not Known	Not Sure	p-value
a. Pap test (conventional cytology)						
0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.424
1-2	5 (41.7)	7 (58.3)	0 (0.0)	0 (0.0)	0 (0.0)	
3-4	23 (37.1)	39 (62.9)	0 (0.0)	0 (0.0)	0 (0.0)	
5 or more	41 (30.4)	90 (66.7)	3 (2.2)	1 (0.7)	0 (0.0)	
b. Pap test (liquid-based cytology e.g., Thin Prep or SurePath®)						
0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.136
1-2	5 (41.7)	7 (58.3)	0 (0.0)	0 (0.0)	0 (0.0)	
3-4	47 (75.8)	13 (21.0)	0 (0.0)	1 (1.6))	1 (1.6)	
5 or more	78 (57.8)	52 (38.5)	0 (0.0)	3 (2.2)	2 (1.5)	
c. HPV DNA test with Pap test						
0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.795
1-2	9 (75.0)	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	
3-4	55 (88.7)	5 (8.1)	0 (0.0)	1 (1.6)	1 (1.6)	
5 or more	109 (80.7)	18 (13.3)	1 (0.7)	5 (3.7)	2 (1.5)	
d. VIA (Visual inspection with acetic acid)						
0	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.449
1-2	6 (50.0	6 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	
3-4	14 (22.6)	46 (74.2)	0 (0.0)	2 (3.2)	0 (0.0)	
5 or more	28 (20.7)	103 (76.3)	0 (0.0)	3 (2.2)	1 (0.7)	
e. VILI (Visual inspection with Lugol's iodine)						
0	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.844
1-2	3 (25.0)	9 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	
3-4	18 (29.0)	37 (59.7)	0 (0.0)	2 (3.2)	5 (8.1)	
5 or more	27 (20.0)	88 (65.2)	5 (3.7)	6 (4.4)	9 (6.7)	

The perceived effectiveness by the participants differed significantly by location of practice for HPV DNA test with Pap test (p-value=0.000). Significantly higher proportion of participants from regions outside NCR reported that HPV DNA test with Pap test was very effective (87.5%) (Table 2c).

Table 2c. Knowledge – Effectivity of different types of screening, by location of practice (n,%)

	Very Effective	Somewhat Effective	Not Effective	Effectiveness Not Known	Not Sure	p-value
a. Pap test (conventional cytology)						
NCR	12 (27.9)	31 (72.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.583
Others	59 (35.1)	105 (62.5)	3 (1.8)	1 (0.6)	0 (0.0)	
b. Pap test (liquid-based cytology e.g., Thin Prep or SurePath®)						
NCR	30 (69.8)	12 (27.9)	1 (2.3)	0 (0.0)	1 (2.3)	0.459
Others	102 (60.7)	60 (35.7)	2 (1.2)	4 (2.4)	2 (1.2)	
c. HPV DNA test with Pap test						
NCR	28 (65.1)	15 (34.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	147 (87.5)	11 (6.5)	1 (0.6)	6 (3.6)	3 (1.8)	
d. VIA (Visual inspection with acetic acid)						
NCR	10 (23.3)	33 (76.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.807
Others	38 (22.6)	124 (73.8)	0 (0.0)	5 (3.0)	0 (0.0)	
e. VILI (Visual inspection with Lugol's iodine)						
NCR	9 (20.9)	32 (74.4)	0 (0.0)	0 (0.0)	2 (4.6)	0.480
Others	39 (23.2)	104 (61.9)	5 (3.0)	8.0 (4.8)	12 (7.1)	

The perceived effectiveness by the participants differed significantly by hospital type for HPV DNA test with Pap test (p-value=0.026). Significantly higher proportion of participants from government hospitals reported that HPV DNA test with Pap test was very effective (87.0%) (Table 2d).

Table 2d. Knowledge – Effectivity of different types of screening, by hospital type (n,%)

	Very Effective	Somewhat Effective	Not Effective	Effectiveness Not Known	Not Sure	p-value
a. Pap test (conventional cytology)						
Government	39 (33.9)	75 (65.2)	1 (0.9)	0 (0.0)	0 (0.0)	0.698
Private	32 (33.3)	61 (63.5)	2 (2.1)	1 (1.0)	0 (0.0)	
b. Pap test (liquid-based cytology e.g., Thin Prep or SurePath®)						
Government	70 (60.9)	41 (35.7)	0 (0.0)	1 (0.9)	3 (2.6)	0.294
Private	62 (64.6)	31 (32.3)	0 (0.0)	3 (3.1)	0 (0.0)	
c. HPV DNA test with Pap test						
Government	100 (87.0)	10 (8.7)	1 (0.9)	1 (0.9)	3 (2.6)	0.026
Private	75 (78.1)	16 (16.7)	0 (0.0)	6 (3.6)	0 (0.0)	
d. VIA (Visual inspection with acetic acid)						
Government	26 (22.6)	97 (75.6)	0 (0.0)	2 (1.7)	0 (0.0)	0.739
Private	22 (22.9)	70 (72.9)	0 (0.0)	3 (3.1)	1 (1.0)	
e. VILI (Visual inspection with Lugol's iodine)						
Government	26 (22.6)	73 (63.5)	4 (3.5)	3 (2.^)	9 (7.8)	0.629
Private	22 (22.9)	63 (65.6)	1 (1.0)	5 (5.2)	5 (5.2)	

In Table 3, it can be seen that 64% performed cervical screening with Pap smear on average-risk females 1-10 times monthly.

Table 3. Cervical Screening performed with Pap Smear on average- risk females monthly

	Frequency	Percentage
0	6	28
1-10	135	64.0
11-20	48	22.8
21-30	8	3.8
31-40	9	4.3
>40	5	2.4
Total	211	

As seen in Tables 4, 5 and 6, majority of participants personally perform the Pap smear (94.3%) and most use conventional cytology (95.3%). The most common material used in performing conventional cytology swab was cytobrush (95.3%) followed by cotton-pledget (51.7%).

Table 7 shows different scenarios where the respondent would indicate a need for Pap Smear or other intervention based on the age, previous Pap smear results, history of the patient. In scenario A, 92,9% responded consistently with the guidelines which indicated no need for Pap smear. In scenario B, 47.9% responded consistently with the guidelines which indicated no need for Pap smear. In scenario C, 29.4% responded consistently with the guidelines which indicated no need for Pap smear. In scenario D, 52.6% responded consistently with the guidelines which indicated Pap smear every 3 years. In scenario E, 51.7% responded consistently with the guidelines which indicated Pap smear every 3 years. In scenario F, 25.6% responded consistently with the guidelines which indicated Pap smear every 3 years. In scenario G, 70.6% responded consistently with the guidelines which indicated no need for Pap smear. In scenario H, 60.2% responded consistently with the guidelines which indicated no need for Pap smear. In scenario I, 37.0% responded consistently with the guidelines which indicated no need for Pap smear. In scenario J, 75.8% responded consistently with the guidelines which indicated no need for Pap smear.

Table 4. Performance of Pap Smear

	Frequency	Percentage
Personally do the Pap Smear	199	94.3
Order for a Pap Smear	104	49.3
Works with Assistant to obtain Pap smear	5	2.4
Total	211	

Table 5. Type of cytology used for screening

	Frequency	Percentage
Liquid-based	56	26.5
Conventional cytology	201	95.3
Others	1	0.5
Don't know	0	0.0
Total	211	

Table 5. Materials used in performing conventional cytology swab

	Frequency	Percentage
Cotton pledget	109	51.7
Cytobrush	201	95.3
Cytobrush with Ayres' spatula	52	24.6
Ayres' spatula	30	14.2
Total	211	

Those with less than 5 years of practice significantly had the highest mean number of responses (6.2±2.0) consistent with guidelines (p-value<0.001) (Table 7a).

The mean number of responses consistent with the guidelines did not vary significantly by number of attendance to CME activities (p-value=0.815) (Table 7b).

Table 7c shows that the mean number of responses consistent with the guidelines did not vary significantly by location of practice (p-value=0.815).

The mean number of responses consistent with the guidelines did not vary significantly by hospital type (p-value=0.2705) (Table 7d). More than half perform HPV DNA testing routinely as recommended (58.8%) (Table 8).

Table 9 shows the interval of both the Pap Test and the HPV DNA test given different scenarios, wherein a previous HPV DNA testing and Pap Smear results were given. For scenario i, the mean interval of Pap test was every 2.9±2.7 years while the mean frequency interval of HPV DNA test was every 3.0±2.9 years. For scenario ii, the mean frequency interval of Pap test was every 1.1±1.2 years while the mean interval of HPV DNA test was every 1.5±1.6 year. For scenario iii, the mean interval of Pap test was every 1.2±1.3 years while the mean interval of HPV DNA test was every 1.3±1.1 year.

The two most common abnormal Pap smear results for which HPV DNA testing was done were ASC-H (70.1%) and ASCUS (69.7%) (Table 10).

Table 11 shows responses to scenarios where the respondent believes that a Pap test is needed to be performed with HPV DNA test and when given HPV vaccine. In scenario A,

Table 7. Results of belief of frequency of Pap smear in different cases (n,%)

Cases/Scenarios	Pap annually (at least for the first 3 years)	Pap every 2 years	Pap every 3 years	Pap > every 3 years	Others	No Pap
a. 18-year old who has never had sexual intercourse and is presenting for her first gynecologic visit	3 (1.4)	3 (1.4)	2 (1.0)	1 (0.5)	6 (2.8)	196 (92.9)
b. 18-year old who had sexual intercourse for the first time 1 month ago and is presenting for her first gynecologic visit	47 (22.3)	10 (4.7)	30 (14.2)	10 (4.7)	13 (6.2)	101 (47.9)
c. 18-year old who first had sexual intercourse 3 years ago and is presenting for her first gynecologic visit	93 (44.1)	8 (3.8)	27 (12.8)	13 (6.2)	8 (3.8)	62 (29.4)
d. 25-year old who has had no new sexual partners in the last 5 years and 3 consecutive negative Pap tests performed by you	40 (19.0)	35 (16.6)	111 (52.6)	18 (8.5)	3 (1.4)	4 (1.9)
e. 35-year old who has had no new sexual partners in the last 5 years and 3 consecutive negative Pap tests performed by you	41 (19.4)	39 (18.5)	109 (51.7)	14 (6.6)	4 (1.9)	4 (1.9)
f. 35-year old who has had no new sexual partners in the last 5 years and 1 negative Pap test performed 12 months ago	133 (63.0)	18 (8.5)	54 (25.6)	5 (2.4)	1 (0.5)	0 (0.0)
g. 35-year old whose cervix was removed last year during hysterectomy for symptomatic fibroids. She has no history of cervical, vaginal, or vulvar dysplasia, and 3 consecutive negative Pap tests performed by you.	7 (3.3)	7 (3.3)	21 (9.9)	23 (10.9)	4 (1.9)	149 (70.6)
h. Healthy 66-year old who has had no new sexual partners in the last 5 years and 3 consecutive negative Pap tests performed by you	10 (4.7)	15 (7.1)	36 (17.1)	21 (9.9)	2 (1.0)	127 (60.2)
i. 66-year old with unresectable nonsmall cell lung cancer and 3 consecutive negative Pap tests performed by you	60 (28.4)	32 (15.2)	21 (9.9)	12 (5.7)	8 (3.4)	78 (37.0)
j. Healthy 71-year old who has had no new sexual partners in the last 5 years and 3 consecutive negative Pap tests performed by you	8 (3.8)	4 (1.9)	19 (9.0)	18 (8.)	2 (1.0)	160 (75.8)

Table 7a. Results of belief of frequency of Pap smear in different cases, by years of practice

Years of practice	Mean number of responses consistent with guidelines	p-value
<5 years	6.2±2.0	<0.001
5 to 10 years	6.3±2.3	
Total	4.5±2.5	

Table 7b. Results of belief of frequency of Pap smear in different cases, by attendance to CME

CME Attendance	Mean number of responses consistent with guidelines	p-value
0	6.5±0.7	0.815
1-2	4.9±2.3	
3-4	5.4±2.4	
5 or more	5.5±2.6	

Table 7c. Results of belief of frequency of Pap smear in different cases, by location of practice

Location of practice	Mean number of responses consistent with guidelines	p-value
NCR	4.9±2.5	0.1181
Others	5.6±2.5	

Table 8. Performance of HPV DNA testing

	Frequency	Percentage
Recommended as routine	124	58.8
Recommend as follow-up test for abnormal Pap	58	27.5
Not recommend at all	29	13.7

Table 9. Interval of Pap test/ HPV DNA test performed

	Interval of Pap Test	Interval of HPV DNA Test
i. Age 35; both HPV DNA test and Pap cytology this year were negative	2.9±2.7 year(s)	3.0±2.9 year(s)
ii. Age 35; HPV DNA test is positive; Pap cytology is negative; both tests were performed this week	1.1 ± 1.2 year(s)	1.5 ± 1.6 year(s)
iii. Age 35; HPV DNA test is negative; Pap cytology shows ASC-US (atypical squamous cells of undetermined significance) cytology; both tests were performed this week	1.2 ± 1.3 year(s)	1.3 ± 1.1 year(s)

Table 10. HPV DNA testing for abnormal Pap smear result

	Frequency	Percentage
ASCUS	147	69.7
ASC-H	148	70.1
LSIL	132	62.5
HSIL	126	59.7
AGC	121	57.3
Total	211	

65.9% (Strongly agree) and 24.2% (Somewhat agree) responded consistently with the guidelines on Pap test with HPV DNA testing. In scenario B, 80.6% (Strongly agree) and 14.2% (Somewhat agree) responded consistently with the guidelines on Pap test with HPV DNA testing. In scenario C, 14.2% (Strongly disagree) and 9.9% (Somewhat agree) responded consistently with the guidelines on Pap test with HPV vaccine. In scenario D, 19.9% (Strongly disagree) and 11.4% (Somewhat agree) responded consistently with the guidelines on Pap test with HPV vaccine.

Table 11. Pap test with HPV DNA testing and HPV Vaccine beliefs (n,%)

	Strongly Agree	Somewhat Agree	Somewhat Disagree	Strongly Disagree	Not Sure
a. A 35-year old woman with no new sexual partners and whose annual Pap tests over the past 5 years were negative should continue receiving annual pelvic exams	139 (65.9)	51 (24.2)	10 (4.7)	11 (5.2)	0 (0.0)
b. HPV DNA testing with Pap testing is more accurate than the Pap test alone in predicting cervical cancer	170 (80.6)	30 (14.2)	0 8 (3.8)	0 (0.0)	3 (1.4)
c. The HPV vaccine will impact when I start cervical cancer screening among females who have been fully vaccinated with the HPV vaccine	112 (53.1)	46 (21.8)	21 (9.9)	30 (14.2)	2 (1.0)
d. The HPV vaccine will impact how often I screen for cervical cancer among females who have been fully vaccinated with the HPV vaccine	85 (40.3)	56 (26.5)	24 (11.4)	42 (19.9)	4 (1.9)

The mean number of responses consistent with the guidelines did not vary significantly by years of practice (p-value=0.1624) (Table 11a).

The mean number of responses consistent with the guidelines did not vary significantly by frequency of attendance to CME activities (p-value=0.2893) (Table 11b).

The mean number of responses consistent with the guidelines did not vary significantly by location of practice (p-value=0.4220) (Table 11c). The mean number of responses consistent with the guidelines did not vary significantly by hospital type (p-value=0.7268) (Table 11d).

Table 12 shows responses of participants when faced with HPV DNA test positive together with abnormal Pap Smear of ASCUS, if they will manage on their own or refer to a different subspecialty. For premenopausal women less than 30 years old with HPV DNA test positive together with abnormal Pap Smear of ASCUS, a little over half of the participants usually manage them on their own (53.5%). For premenopausal women 30 years or older with HPV DNA test positive together with abnormal Pap Smear of ASCUS, more than half of the participants (55.9%) refer them to another subspecialty. For post-menopausal women with HPV DNA test positive together with abnormal Pap smear of ASCUS, more than two-thirds of the participants (67.3%) refer them to another subspecialty.

In the previous year, 37.0% reported having 1 to 5 patients who requested to be tested with HPV DNA testing (Table 13).

Table 11a. Pap test with HPV DNA testing and HPV Vaccine beliefs, by years of practice

Years of practice	Mean number of responses consistent with guidelines	p-value
<5 years	2.5±0.9	0.1624
5 to 10 years	2.2±0.8	
Total	2.4±1.0	

Table 11b. Pap test with HPV DNA testing and HPV Vaccine beliefs, by attendance to CME

Years of practice	Mean number of responses consistent with guidelines	p-value
0	2.5±0.7	0.2893
1-2	2.2±0.6	
3-4	2.6±0.8	
5 or more	2.3±1.0	

Table 11c. Pap test with HPV DNA testing and HPV Vaccine beliefs, by location of practice

Years of practice	Mean number of responses consistent with guidelines	p-value
NCR	2.3±0.7	0.4220
Others	2.4±0.9	

Table 11d. Pap test with HPV DNA testing and HPV Vaccine beliefs, by hospital type

Years of practice	Mean number of responses consistent with guidelines	p-value
Government	2.4±1.0	0.7268
Private	2.4±0.8	

Table 12. HPV DNA test positive together with abnormal Pap Smear of ASCUS (n,%)

	Manage on my own	Refer to another subspecialty
a. Premenopausal, < 30 years old	113 (53.5)	98 (46.5)
b. Premenopausal, >= 30 years old	93 (44.1)	118 (55.9)
c. Postmenopausal	69 (32.7)	142 (67.3)

Table 13. In the previous year, did patients ask if they should be tested with HPV DNA testing?

	Frequency	Percentage
YES	78	37.0
1-5	78	100.0
5-10	0	0.00
10-15	0	0.00
>15	0	0.00
NO	133	63.0
Total	211	

DISCUSSION

More than 99 percent of all cervical cancer cases are associated with persistent infection with human papillomavirus (HPV)[1]. The precancerous stage and the time window from dysplasia to carcinoma is long, with an average of 10 years. Because of these reasons, prevention of cervical cancer through screening can be done effectively. There are several methods to screen cervical cancer, such as Pap smear, visual inspection with acetic acid, and HPV DNA testing, among others.[6]

This research gathered information on the knowledge and practices of Obstetricians and Gynecologists on cervical cancer screening. Our study showed that out of 10 scenarios, the mean number of responses consistent with the guidelines for frequency of Pap smear was only 5.5±1.9. This score was

found to vary in terms of years of practice wherein those with shorter years of practice had more responses consistent with the guidelines. This can be because those with shorter years of practice have just recently finished their residency or fellowship training and so are more updated with the newer guidelines. In contrast, those with longer years of practice may be more familiar with older guidelines. Also, it is possible that their knowledge on cervical cancer screening may have been affected by their personal experience while practicing their profession. In a similar study conducted among Jordanian gynecologists, it was seen that the majority (77.4% of the 392 participants) agreed that the role HPV in the causation of pre-invasive and invasive carcinoma of the cervix is well established.[7] On the other hand, 48.5% of the participants agreed that Pap smear is the most cost-effective public health tool for cervical cancer screening while 44.3% agreed that increased sensitivity in cervical cancer screening can be seen when Pap smear and HPV tests are combined.[8] In another study conducted in the Western Region of Saudi Arabia, 91% of 200 physicians knew that the Pap smear test is used as a screening method for cervical cancer, while only 48.5% of the physicians knew about the HPV vaccine.[9] In a survey conducted in 2006 to 2007, a smaller percentage (25%) of participants (n= 1212) completely agreed with guideline recommendations on cervical cancer screening.[10] The results can reflect lack of knowledge of the value of Pap smear as a tool for cervical cancer screening, or a belief that Pap smear has low sensitivity as cervical cancer screening tool.

The American College of Obstetrics and Gynecology (ACOG), the U.S. Preventive Services Task Force and the American Society for Colposcopy and Cervical Pathology (ASCCP), all internationally recognized bodies, currently recommend cervical screening with cytology to be performed every 3 years among women starting 21 years of age. For women with ages of 30 to 65-years-old, cervical cytology alone; HPV testing alone, and co-testing of cervical cytology and HPV testing are recommended every 3, 5, and 5 years, respectively. The 2020 World Health Organization (WHO) recommendation for cervical cancer screening and the 2020 ACS Guidelines for the prevention of cervical cancer puts an emphasis on the importance of primary HPV testing, which means they can be used alone rather than with a simultaneous Pap Smear.[4] HPV testing distinguishes infection by high-risk types of HPV, which are more likely to cause precancerous lesions of the cervix and cervical cancers. More so, no screening is recommended among women with age 65 years above and has adequate prior screening.[11] In a cross-sectional survey conducted in 2006 to 2007, majority (91%) of the 1212 physicians included in the survey reported providing Pap smear to their eligible patients.[10] It can also be noted that among those who provide Pap smear (n= 1114), screening practices, including number of tests ordered or performed, use of patient reminder systems, and cytology method used, significantly varied by physician specialty (p-value< 0.001). More than 75% of obstetrician-gynecologists ordered or performed more than 40 Pap tests per month, compared with 5.2% of internists and 12.7% of general or family practice physicians[2]. Almost 95% of all physicians recommended Pap smear at least every 3 years for the 18-year old woman who became sexually active 3 years ago.On the other hand, 42.4% of physicians recommended Pap smear annually for women aged 25-year old women with no new sexual partners in the past 5 years and 3 consecutive negative Pap smear results. The results of the current survey showed that 52.6% of the participants screen women with age 25 years every 3 years. Comparing the results from the study conducted among Jordanian gynecologists, only 46% perform the Pap Smear on a 3-yearly basis. The study explained it as the majority of Jordanians are Muslims and it was a perceived association between HPV and promiscuity, they do not consider women to be at risk, since Muslim women are usually monogamous. The performance of Pap Test doubled from this study at 95% compared to the Jordanians at 46%.[7] This reflects the practice of obstetrician-gynecologists in our setting follows the set guidelines more. These differences may be cultural.

Different factors may affect the knowledge and practice of obstetrician-gynecologists on cervical cancer screening. In a survey conducted by Yabroff et al., those who are practicing at an urban location (p-value< 0.001), and had continuing medical education on cervical cancer screening within 3 years (p-value= 0.003) were significantly associated with increased Pap smear screening practice and beliefs.10 Ferdous et al. reported that in Bangladesh despite approximately 40.9% of female doctors having good knowledge on cervical cancer screening, only 8.8% of the female doctors did not ever have a screening test for the said disease. It can also be noted that the older the physicians were, the greater was their knowledge score on cervical cancer screening (p-value< 0.001). More so, participants having good knowledge score screened more (40.9%) than those having poor knowledge score (2.8%) (p-value< 0.001).[12] In a separate survey conducted by Kress et al. among 333 health care workers in Ethiopia, some of the reported barriers to performing cervical cancer screening were lack of training (52%) and resources (53%).[13] In the current study, it was seen that years in practice, location of practice, and type of institution affiliated to are significant factors that may affect knowledge and practice on cervical cancer screening.

Additional results of our study showed that 58.8% of the participants routinely included HPV testing as part of the cervical cancer screening. Guideline recommendations do not suggest using Pap smear or HPV test results to determine whether HPV vaccine should be given to unvaccinated woman.[11] In a previous study conducted, Malo et al. reported that 66% of family physicians and obstetrician-gynecologists (n= 574) included in their survey often or always recommended vaccination to patients with an abnormal Pap smear result, and 77% did not plan to change Pap screening frequency for vaccinated females. Also, 80% correctly reported rarely or never using HPV testing results to guide vaccine recommendations.[14] Lataifeh et al. explained that either lack of knowledge of the value of the HPV test, or the lack of the availability of the test affects the knowledge and practice on HPV screening in connection to cervical cancer screening.[7] Only approximately 60% routinely included the HPV testing in our country. This may be attributed to the lack of familiarity of the practicing obstetrician-gynecologists and the high cost of the HPV testing. This is paid for, out-of-pocket, by the women rather than it being an available universal screening tool subsidized by the government. The WHO recommends in all countries that 70% of women be HPV-tested by age 35 years and again in 45 years of age to eradicate cervical cancer as a public health problem.[15] Aside from the cost of the HPV DNA testing, another barrier is the sparsity of laboratories offering the processing of this test. For third-world and resourceconstrained countries, an alternative approach is visual inspection with acetic acid followed by treatment if necessary. Although this

method can be easily done and is widely available, this is heavily subjective thus has variable sensitivity.

Clinicians are highly aware of the importance of cervical cancer screening. However, to be maximally effective, these screening parameters should be scaled to the national level, through the healthcare system, which should be made available to all population, especially to the underprivileged. Forward action must concentrate to the evidence-based interventions (cervical cancer screening, HPV DNA testing, and vaccination) to eliminate cervical cancer as one of our country's problem.[15]

This study determined the knowledge and practices on cervical cancer screening among Philippine Obstetrical and Gynecological Society – accredited Obstetricians and Gynecologists practitioners in the country. A strength of this study is the large number of participants coming from 26 institutions from different regions of the country. This improves the generalizability of the study findings. A limitation of this study however is the risk for responder's bias wherein participants may respond differently with regards to their practice because of poor recall or a tendency to adhere to what is theoretically right.

CONCLUSION

The level of knowledge of POGS-accredited OB-GYNS with regard cervical cancer screening is varied as seen from the consistency with the guidelines of their responses. In our study, the rates of responses consistent with the guidelines in frequency of Pap smear varied greatly from 25.6% to 92.9%. On the other hand, the rates of responses consistent with the guidelines in Pap smear test with HPV DNA testing and HPV Vaccine varied from 24.1% to 90.1%. Also, the HPV DNA testing was routinely performed as recommended by some participants only. The practice of referring abnormal Pap smear findings with HPV DNA test positive also variedly greatly among the participants. Years in practice, location of practice and type of institution affiliated to are significant factors that may affect knowledge and practice on cervical cancer screening.

RECOMMENDATIONS

Further studies are recommended to explore additional factors which causes variation in practice of cervical cancer screening in the country. Obstetricians and Gynecologists practitioners need to improve and update their knowledge on cervical cancer screening so that their practice will follow such and be consistent with the latest guidelines. Also, the healthcare system of our country will hopefully shoulder the cost of the evidence-based interventions (cervical cancer screening, particularly HPV DNA testing, and vaccination) that will bring down the incidence cervical cancer in the country. ■

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Adjuvant therapy for stage IA endometrioid endometrial cancer with lymphovascular space invasion

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ABSTRACT

Background: In the Philippines, endometrial cancer was estimated to be the 13th most common in both sexes (2%), and the 8th leading site among women (4%) in 2015. There were estimated 2,451 new cases and 565 deaths in that year.

Objective: To determine the outcomes of patients with endometrial cancer, endometrioid type, stage IA, grade 1 or 2, with lymphovascular space invasion (LVSI) who were given adjuvant therapy of pelvic external beam radiation therapy (EBRT), vaginal brachytherapy and chemotherapy from 2012-2018.

Methodology: This is a 7-year retrospective analysis of patients with endometrial cancer, endometrioid type, stage IA, grade 1 or 2, with LVSI who were given adjuvant therapy of either pelvic EBRT, vaginal brachytherapy or chemotherapy after undergoing peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingo-oophorectomy, pelvic lymph node dissection, with paraaortic lymph node sampling. Data from the outpatient department weekly census from January 1, 2012 to December 31, 2018 in a single tertiary government hospital were extracted. The clinico-pathologic characteristics and adjuvant therapy of the eligible patients were identified. The recurrence rate, progression-free survival and overall survival of the patients who received adjuvant therapy of pelvic EBRT, vaginal brachytherapy and chemotherapy was compared.

Results: The median age was 52 years. The overall LVSI rate in 339 patients was 13.6% (n=46). None of the patients underwent vaginal brachytherapy. For those who underwent chemotherapy, three (7.9%) patients had documented recurrence. No significant difference in recurrence rate was found between chemotherapy and EBRT. None of the patients who underwent pelvic EBRT experienced toxicities. The rate of toxicity was significantly higher in those who had chemotherapy compared to EBRT

Conclusion: LVSI was said to be usually found in those with poorly-differentiated tumors with deep invasion. In a Gynecologic Oncology Group (GOG) study, 15% (93) had LVSI in 621 patients. Pelvic node metastasis was 27%, while paraaortic node metastasis was 19% in those with LVSI, compared to 7% and 3% respectively in those without. The recurrence rate is increased at 44% for those with LVSI versus 2% for those without. The GOG has suggested that LVSI is an important risk factor in risk models predicting risk of recurrence in node-negative, early-stage endometrial cancer. In the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC) trial, LVSI was a factor associated with distant site of failure.

Keywords: *Endometrial cancer, high-intermediate risk, lymphovascular space invasion, adjuvant therapy, pelvic external beam radiation therapy, vaginal brachytherapy, chemotherapy*

INTRODUCTION

Background and Significance

In the Philippines, endometrial cancer was estimated to be the 13th most common in both sexes (2%), and the 8th leading site among women (4%) in 2015. There were estimated 2,451 new cases and 565 deaths in that year. In 2012, the estimated age-standardized national incidence rate was 5.6 per 100,000. One (0.5) out of 100 women would have had a likelihood of getting endometrial cancer before age 75. The estimated national standardized mortality rate was 1.4 per 100,000. Less than one (0.1) out of 100 women would have died from endometrial uteri cancer before age 75.[1]

Endometrial cancer represents the second most common reason for new consults (24.1%) and overall consults (22.4%) following cervical cancer in a tertiary institution.[2] Endometrioid adenocarcinoma is the most common histologic type of endometrial cancer (84%). Most patients present with Stage I tumors (73%), with a 5-year survival of 81 – 91%. [3,4]

Studies show that lymphovascular space involvement (LVSI) is associated with recurrence even in early-stage cancers.[4] Patients with stage IA, grade 1 and 2 tumors, with LVSI are classified under the high-intermediate risk group. As of the present time, international recommendation promotes EBRT or vaginal brachytherapy as adjuvant therapy for these patients.[5,6] On the other hand, local recommendation places equal footing on vaginal brachytherapy, pelvic external beam radiotherapy and chemotherapy. The final decision lies in the clinician's preference and experience.[7] The adjuvant therapy for patients with early-stage tumors with LVSI should represent the choice balancing recurrence and toxicities. In the institution where the study was conducted, the traditional preference was to give chemotherapy.

There has been no local study conducted comparing the outcomes of the three modalities as adjuvant treatment for patients with the subset of patients with stage IA disease but with LVSI. Identification of the modality with the best outcome may lead to future recommendations regarding the preference of treatment in this subset of patients.

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Financial Disclosure:
The authors did not report any potential conflicts of interest.

Figure 1 depicts the conceptual framework of the study.

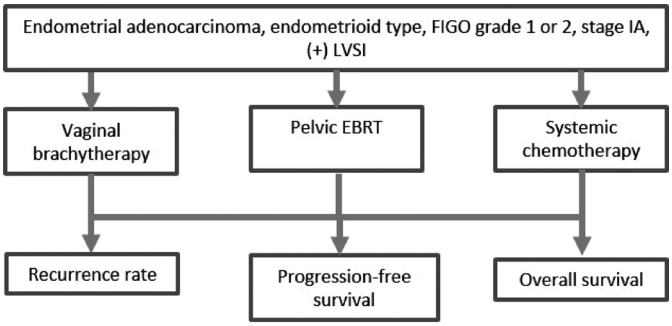

Figure 1. Conceptual framework

Operational Definition of Terms

Architectural grading was based on the degree of glandular differentiation in accordance with the FIGO guidelines.

LVSI, as reported in the histopathology result, means tumor cells were within or attached to the wall of a capillary-like space.

Recurrence is presence of tumor after all gross tumor was excised with the margins of the specimen free from disease. It may be local (vagina, vaginal vault or pelvic sidewall, locoregional (pelvic and/or paraaortic lymph nodes, peritoneum or pelvic viscera) or distant (omentum, liver, lung, bone and brain).

Persistence after surgery is presence of tumor in the operative field or local recurrence within one year of initial surgery.

Progression-free survival is the length of time during or after the treatment of a disease that a patient lives without worsening of the malignancy.

Overall survival is the length of time that a patient survives from the start of treatment.

OBJECTIVES

General Objective

To determine the treatment outcomes of patients with endometrial cancer, endometrioid type, stage IA, grade 1 or 2, with LVSI who were given adjuvant therapy of pelvic EBRT, vaginal brachytherapy and chemotherapy from 2012-2018.

Specific Objectives

A. To describe the clinic-pathologic characteristics of patients with endometrial cancer, endometrioid type, stage IA, grade 1 or 2, with LVSI
B. To determine the recurrence rate, progression-free survival and overall survival in five years of patients with endometrial cancer, endometrioid type, stage IA, grade 1 or 2, with LVSI who were given adjuvant therapy of pelvic EBRT, vaginal brachytherapy and chemotherapy
C. To compare the progression-free survival and overall survival in five years of patients with endometrial cancer, endometrioid type, stage IA, grade 1 or 2, with LVSI who were given adjuvant therapy of pelvic EBRT, vaginal brachytherapy and chemotherapy

MATERIALS AND METHODS

Study Design

This is a 7-year retrospective analysis of patients with endometrial cancer, endometrioid type, stage IA, grade 1 or 2, with LVSI who were given adjuvant therapy of pelvic EBRT, vaginal brachytherapy and chemotherapy after undergoing peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingo-oophorectomy, pelvic lymph node dissection, with paraaortic lymph node sampling. Data from the outpatient department weekly census from January 1, 2012 to December 31, 2018 in a single tertiary government hospital was extracted. The clinico-pathologic characteristics and adjuvant therapy of the eligible patients were identified. The incidence of recurrence, progression-free survival and overall survival of the patients who received adjuvant therapy were determined and compared.

Ethical Considerations

This study was approved by the University of the Philippines Manila Research Ethics Board.

Inclusion and Exclusion Criteria

Women eligible for participation included those:

- Who underwent primary peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, paraaortic lymph node sampling for endometrial cancer
- On final histopathology result, with endometrial cancer, endometrioid type, stage IA following the 2009 FIGO staging system for endometrial cancer, grade 1 or 2, with LVSI.

Exclusion criteria included those:

- Who received pelvic radiation and/or chemotherapy prior to surgery
- With serous, clear cell or sarcomatous histology, those with synchronous tumors (two primary tumors diagnosed within 6 months), and patients diagnosed with another cancer before the diagnosis of endometrial cancer
- With incomplete data on histopathology (LVSI status) and adjuvant treatment (details on the adjuvant treatment received)

Data Collection Procedure

All patients who satisfied the inclusion criteria based on the outpatient department weekly census from January 1, 2012 to December 31, 2018 was identified. Hence, there was no sample size to be presented.

All data from the eligible patients' charts, intraoperative reports and histopathologic reports was manually encoded into an electronic spread sheet file and was checked for consistency and completeness. For each of the patients included, the following data will be extracted: (1) Demographics: age, height, weight, body mass index (BMI); (2) procedure performed, tumor grade, number of pelvic and paraaortic lymph nodes harvested based on final histopathologic report, (3) types of adjuvant therapy (4) onset (from time of surgery, in months) and location of recurrence if present, and (5) total period (from time of surgery, in months) with no evidence of disease for those without recurrence.

Algorithm

Figure 2 depicts the algorithm for the methodology of this study.

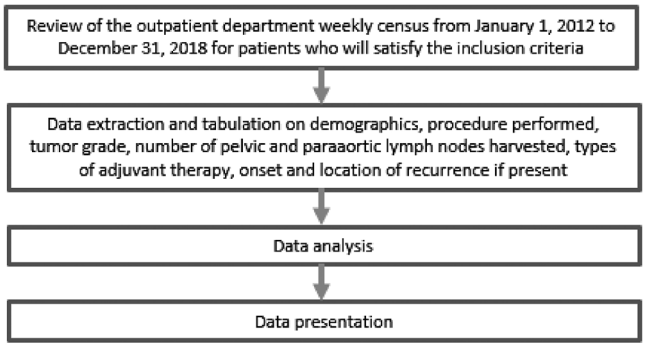

Figure 2. Methodology algorithm

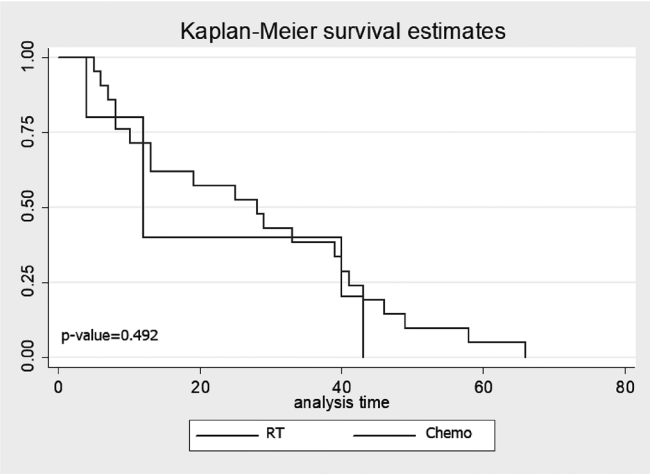

Figure 3. Progression-free survival of pelvic EBRT versus chemotherapy

Data Analysis

Data analysis was carried out using Stata 14. Descriptive statistics such as mean, median, standard deviation were used for numerical data variables, while frequency and percentage will be used for categorical variables. Kaplan-Meier method was used to describe survival curves of the adjuvant treatments. Cox proportional hazards regression analysis was be used to compare PFS and OS among the adjuvant treatments. A P-value of < 0.05 will be considered significant.

RESULTS

The median age was 52 years. The median gravidity was 3 and median parity was 1. The median BMI was 25. The more common tumor grade was grade 2 (62.2%) compared to grade 1 (37.8%).

The overall LVSI rate in 339 patients was 13.6% (n=46). Thirty-eight patients (82.6%) had the adjuvant therapy of chemotherapy in the form of Carboplatin (AUC 5 – 6) and Paclitaxel (175 mg/m^2) every 21 days for six cycles. Seven (15.2%) out of 46 had pelvic EBRT. None of the patients underwent vaginal brachytherapy.

For those who underwent chemotherapy, three (7.9%) patients had documented recurrence: one at 8 months to the left internal iliac nodes, one at 12 months to the pelvis and one at 18 months to the pelvic bone. For those who underwent pelvic EBRT, one (1.4%) patient had a documented recurrence at 12 months to the lungs. No significant difference in recurrence rate was found between chemotherapy and EBRT (risk ratio=0.55, 95% CI = 0.06 to 4.6, p-value=0.306).

The median PFS was 26 months. The median PFS did not differ significantly between those who underwent RT (19 months), and chemotherapy (24 months) (p-value=0.492) as shown in Figure 3.

Data on overall survival was not available due to the loss to follow-up of majority of patients after they were disease-free.

None of the patients who underwent pelvic EBRT experienced toxicities. On the other hand, 31.6% (12, 95% CI = 19.1 - 47.5, p-value<0.001) patients who underwent chemotherapy in the form of neutropenia, transaminesemia, and anemia. The rate of toxicity was significantly higher in those who had chemotherapy compared to EBRT.

DISCUSSION

LVSI was said to be usually found in those with poorly-differentiated tumors with deep invasion. In a Gynecologic Oncology Group (GOG) study, 15% (93) had LVSI in 621 patients. Pelvic node metastasis was 27%, while paraaortic node metastasis was 19% in those with LVSI, compared to 7% and 3% respectively in those without. The recurrence rate is increased at 44% for those with LVSI versus 2% for those without. The GOG has suggested that LVSI is an important risk factor in risk models predicting risk of recurrence in node-negative, early-stage endometrial cancer. In the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC) trial, LVSI was a factor associated with distant site of failure.[3]

In a retrospective study in 2015 involving endometrial cancer patients with grade 1 or 2 endometrioid histology, myometrial invasion less than 50%, and disease confined to the uterus, recurrence-free survival (RFS) and overall survival (OS) were calculated in those with LVSI and those without. A total of thirty patients (12.5%) received adjuvant therapy. Patients with LVSI were more likely to have myometrial invasion (P < 0.001), postoperative pathologic grade 2 disease (P < 0.001), to undergo lymphadenectomy (P = 0.049) and receive adjuvant therapy (P < 0.001). The 5-year cumulative incidence of recurrence was 14.2% in the LVSI group (P = 0.053) versus 3.8% in the no-LVSI group. LVSI was significantly associated with worse RFS (P = 0.002) and OS (P = 0.013) in spite of being more likely to undergo lymphadenectomy and adjuvant treatment. In summary, LVSI is noted to be an independently significant prognostic factor.[4]

In this study, the overall LVSI rate in 339 patients with stage IA, grade 1 an 2 tumors, was 13.6%. This is close to the value of 12% and 16.7% obtained in the studies of O'Brien et al and dos Reis et al. [8,9]

In the ESGO/ESTRO/ESP Guidelines for Management of Patients with Endometrial Carcinoma in 2020, stage I endometrioid with substantial LVSI regardless of grade and depth of invasion is classified under the high-intermediate risk group. Other patients included in the high-intermediate risk group are those with stage IB endometrioid high-grade regardless of LVSI status and stage II tumors.[5]

The PORTEC-3 trial was an open-label, international, randomized, phase 3 trial involving 103 centers in six clinical trials collaborating in the Gynecological Cancer Intergroup.

Table 1. Characteristics of patients with Endometrioid Endometrial Cancer who had LVSI

	With LVSI=46
Age in years (median, range)	52 (23-68)
Gravidity (median, range)	3 (0-4)
Parity (median, range)	1 (0-3)
BMI (median, range)	25 (16.8-32.9)
Tumor Grade	
1	17 (37.8%)
2	28 (62.2%)
Adjuvant therapy	
Pelvic EBRT	7 (15.2%)
Chemotherapy	38 (82.6%)
Follow-up time with no evidence of disease (median, range)	26 (4-85)

There were 660 eligible women with high-risk endometrial cancer with FIGO 2009 stage I, endometrioid-type grade 3 with deep myometrial invasion or lymph-vascular space invasion (or both), endometrioid-type stage II or III, or stage I to III with serous or clear cell histology. Women were randomly assigned to receive radiotherapy alone (48.6 Gy in 1.8 Gy fractions given 5 days weekly) or radiotherapy and chemotherapy (two cycles of cisplatin 50 mg/m² given during radiotherapy, followed by four cycles of carboplatin AUC 5 and paclitaxel 175 mg/m). 5-year overall survival was 81.8% (95% CI 77.5 – 86.2) with chemoradiotherapy versus 76.7% (72.1–81.6) with radiotherapy (adjusted hazard ratio [HR] 0·76, 95% CI 0.54 – 1.06; p=0.11); 5-year failure-free survival was 75.5% (95% CI 70.3 – 79.9) versus 68.6% (63.1–73.4; HR 0·71, 95% CI 0.53 – 0.95; p=0.022). Grade 3 or worse adverse events during treatment occurred in 198 (60%) of 330 who received chemoradiotherapy versus 41 (12%) of 330 patients who received radiotherapy (p<0.0001). Adjuvant chemotherapy given during and after radiotherapy for high-risk endometrial cancer increased failure-free survival but did not improve 5-year overall survival.[10]

The GOG-249 trial was a randomized phase III trial performed in 601 eligible patients with International Federation of Gynecology and Obstetrics (2009) stage I endometrioid histology with Gynecologic Oncology Group protocol 33–based high-intermediate–risk criteria, stage II disease, or stage I to II serous or clear cell tumors. Treatment was randomly assigned between RT (45 to 50.4 Gy over 5 weeks) or vaginal cuff brachytherapy followed by intravenous paclitaxel 175 mg/m^2 (3 hours) plus carboplatin (AUC 6) every 21 days for three cycles. With a median follow-up of 53 months, the 60-month RFS was 0.76 (95% CI, 0.70 to 0.81) for RT and 0.76 (95% CI, 0.70 to 0.81) for VCB/C (hazard ratio, 0.92; 90% confidence limit, 0.69 to 1.23). The 60-month overall survival was 0.87 (95% CI, 0.83 to 0.91) for RT and 0.85 (95% CI, 0.81 to 0.90) for VCB/C (hazard ratio, 1.04; 90% confidence limit, 0.71 to 1.52). Vaginal and distant recurrence rates were similar between arms. Pelvic or para-aortic nodal recurrences were more common with VCB/C (9% v 4%). Vaginal brachytherapy plus chemotherapy was not superior to pelvic RT. Acute toxicity was greater with vaginal brachytherapy plus chemotherapy but late toxicity was similar. The study concluded that pelvic RT alone remains an effective, well-tolerated, and appropriate adjuvant treatment in high-risk early-stage endometrial carcinomas of all histologies.[11]

There were no patients who underwent vaginal brachytherapy in the study. Still, there was no statistically significant difference in the recurrence rate and progression-free survival of the patients who underwent pelvic EBRT or chemotherapy. The sample size of 46 was too small to make sufficiently powered statistical analysis to detect possible differences in outcomes across groups.

Statistically, toxicities were significantly higher in those who had chemotherapy compared to pelvic EBRT. This finding was also consistent with PORTEC 3 and GOG 249.

Current recommendations regarding the adjuvant treatment of early-stage endometrial cancer with LVSI are variable. The National Comprehensive Cancer Network 2021 endorses vaginal brachytherapy.[6]

On the other hand, the recent ESGO/ESTRO/ESP Guidelines acknowledged the higher risk of recurrence in the high-intermediate risk group (even with negative nodes) and adjuvant brachytherapy can be recommended to decrease vaginal recurrence. In the specific case of substantial LVSI, pelvic EBRT can be considered as it has been shown to reduce the risk of pelvic and para-aortic nodal relapse. Omission of adjuvant treatment is an option and this should be considered only when close follow-up is guaranteed to ensure detection and prompt treatment of recurrence at an early stage.[5]

Locally, the Society of Gynecologic Oncologists of the Philippines, in its Clinical Practice Guidelines in 2019, recommends vaginal brachytherapy or pelvic EBRT or chemotherapy.[7]

The results of this study seem to favor pelvic EBRT such that it had no toxicities compared chemotherapy even if both treatments had no significant difference in terms of recurrence rate and progression-free survival.

CONCLUSION

In patients with stage IA endometrioid endometrial cancer FIGO grades 1 and 2, the overall lymphovascular space invasion rate is 13.6%. These patients underwent pelvic EBRT or chemotherapy. There were no patients who were given vaginal brachytherapy. Due to the limited sample size of 46, the findings of this study did not provide evidence that the type of adjuvant therapy (pelvic EBRT or chemotherapy) affects recurrence rate or progression-free survival. Overall survival was not obtained because of the loss of follow-up of majority of patients. Toxicities were significantly higher in those who had chemotherapy compared to pelvic EBRT. Clinicians should be aware of potential adverse events including neutropenia, transaminesemia, and anemia, in choosing the adjuvant treatment for patient.

It is recommended to extend the years included in the study to provide more samples and consequently a more powerful statistical analysis. In addition, a randomized control trial comparing the outcomes of pelvic EBRT, vaginal brachytherapy and chemotherapy, would provide better data on recurrence rate, progression-free survival and overall survival.

It is also advised the record keeping and mechanism of following up of patients should also be improved in the institution so that data on overall survival could be obtained. ■

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Clinical Characteristics, Treatment Response and Prognosis of Locally Advanced Adenocarcinoma of the Cervix: A Local Study

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ABSTRACT

Background: Treatment of cervical carcinoma regardless of histology, either, squamous carcinoma, adenocarcinoma or adenosquamous carcinoma is the same, concurrent chemoradiotherapy. Nevertheless, studies have different and contradictory results. The current study sought to determine clinical characteristics, treatment response and prognosis of locally advanced adenocarcinoma of the cervix in comparison to squamous cell carcinoma.

Methods: Outpatient charts of the cervical cancer patients from the outpatient department of Section of Gynecologic Oncology of a tertiary hospital were retrospectively reviewed.

Results: Among the 979 charts reviewed, only 278 patients were included in the analysis. Seventy-five percent of the patients had squamous cell carcinoma and only 20% had adenocarcinoma. Baseline characteristics were comparable. Ninety-eight percent had Cisplatin-based concurrent chemoradiotherapy. Median follow up was 17 months, with 75% of the patients had complete response and 16% had recurrent disease. Most common site of recurrence was cervix, lungs and bones. Disease free survival and overall survival was the same for adenocarcinoma and squamous cell carcinoma.

Conclusion: Patients with locally advanced adenocarcinoma of the cervix who underwent concurrent chemoradiation had the same treatment response and prognosis to patients with squamous cell carcinoma.

Keywords: Cervical carcinoma, adenocarcinoma, squamous cell carcinoma

INTRODUCTION

Cervical cancer remains to be a major disease burden especially in low resource countries. In 2018, cervical cancer ranked fourth as the cause of cancer in women, after breast, colorectal and lung cancer. It was also the fourth primary cause of cancer associated death in women. About 570,000 women developed cervical cancer and 311,000 died from it, with an age standardized incidence rate of 13.1 per 100,000 and age standardized mortality rate 6.9 per 100,000. Southeast Asia has a very high burden of disease, with an age standardized incidence rate of ≥15 per 100,000.[1]

In the Philippines, cervical cancer rank as the second leading cause of cancer among women ages 15 to 44 years old with an age standardized incidence rate of 14.9. It is also the third leading cause of cancer associated death among women ages 15 to 44 years old; with an age standardized mortality rate of 8.8.[2] The incidence of cervical cancer and of squamous cell carcinoma had progressively decreased in the developed countries, in contrast to the increasing incidence of adenocarcinoma.[3] In 2019, 339 new cases were seen at our institution, more than half (64.6%) were diagnosed as stage IIIB.[4] By histology, the age-standardized incidence rates in the Philippines by Manila cancer registry from 2008-2012 are as follows: squamous cell carcinoma 7.4, adenocarcinoma 2.7, others 0.4, and unspecified 1.0.[2]

The impact of cervical tumor histology in terms of response to treatment and survival still is a topic of consideration and with contradictory results. Study by Galic et. al., stated that patients with cervical adenocarcinoma have a poorer overall survival.[5] While a study presented by Katanyoo, adenocarcinoma, adesquamous and squamous cell carcinoma have a similar outcome when treated with the standard concurrent chemoradiotherpy.[6] Currently, based on the Clinical Practice Guidelines of the Society of Gynecologic Oncologists of the Philippines, adenocarcinomas have not shown significant difference in clinical behavior from squamous cell carcinoma, thus, treatment guidelines for squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma are the same.[7]

This study was designed to retrospectively determine the clinical characteristics, treatment response and prognosis of locally advanced adenocarcinoma of the cervix in comparison to squamous cell carcinoma who underwent the standard concurrent chemoradiotherapy.

OBJECTIVES

The retrospective study aimed to determine the clinical characteristics, treatment response and prognosis of locally advanced adenocarcinoma of the cervix in a local setting.

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Financial Disclosure:
The authors did not report any potential conflicts of interest.

General Objective

The objective of this study is to determine the clinical characteristics, treatment response and prognosis of locally advanced adenocarcinoma of the cervix who underwent concurrent chemoradiotherapy with weekly Cisplatin or Carboplatin in comparison to squamous cell carcinoma.

Specific Objectives

1. To determine the clinic-pathologic profile of patients with locally advanced adenocarcinoma of the cervix.
2. To determine the treatment response of patients with locally advanced adenocarcinoma of the cervix who underwent concurrent chemoradiotherapy with weekly Cisplatin or Carboplatin.
3. To determine the prognosis of patients with locally advanced adenocarcinoma of the cervix who underwent concurrent chemoradiotherapy with weekly Cisplatin or Carboplatin.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board; patient's charts from the outpatient Section of Gynecologic Oncology and Trophoblastic Diseases of cervical cancer patients with locally advanced stage treated with concurrent chemoradiotherapy from 2015 to 2019 were reviewed. Inclusion criteria included the following: histologically proven cervical carcinoma of either squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; International Federation of Gynecology and Obstetrics (FIGO) 2009 and 2018 stage IB3, IIA2 to IVA; treated and completed pelvic external beam radiotherapy followed by brachytherapy with weekly Cisplatin or Carboplatin. Patients with neuroendocrine, adenoma malignum or other rare histology; early stage (IA1, IA2, IB1, IB2); those with proven distant metastasis; and with incomplete radiotherapy and records were excluded from the study.

Patients were treated with pelvic external beam radiotherapy with concurrent Cisplatin 40 mg/m^2 weekly or Carboplatin 300 mg/m^2 every 3 weeks or 60-90 mg/m^2 weekly followed by brachytherapy. Patient's hematological, renal, and liver function were monitored weekly as well as the status of serum electrolytes and presence of urinary tract infection. In a study done by Rose et. al. showed that radiotherapy with concurrent platinum containing chemotherapy (Cisplatin) improved survival and progression free survival among women with locally advanced cervical cancer.[8] Another study done by Higgins et al, showed that patients with locally advanced cervical cancer can be given Carboplatin concurrently with radiotherapy also has 90% complete response rates.[9]

Patient was seen at the Gynecologic Oncology Outpatient Department weekly during the treatment for monitoring of tumor response and evaluation of treatment toxicity. Then, patient follow up two weeks post-treatment. Followed by monthly surveillance for 3 consecutive months. Then succeeding follow up was as follow: every 3 months for the first 2 years; every 6 months from the third year to the firth year; and annually thereafter. Follow up visits included pertinent history taking regarding signs of recurrence, physical examination with emphasis on clinically palpable lymph nodes (supraclavicular and inguinal nodes) and pelvic examination; annual whole abdominal CT scan for surveillance and other ancillary studies as needed.

The endpoints included treatment response, overall survival and disease free survival. Treatment response includes: complete response which was defined as no residual tumor found on pelvic examination; partial response was defined as decreased of 50% in the cervical tumor size clinically; stable disease defined as decreased of less than 50% in the cervical tumor size clinically; progression was defined as increased in the cervical tumor size or radiographic documentation of distant metastasis during treatment; recurrence defined as re-appearance of tumor after treatment either in the pelvic area or at distant sites. Disease free survival defined as the duration from the first day of completed treatment to the time of tumor recurrence, either pelvic or at distant sites. Overall survival defined as from the first day of treatment to the time of death.

For data analysis descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. One-way ANOVA, Kruskal-Wallis test and Fisher's Exact test was used to determine the difference of mean, median and frequency, respectively. Kaplan-Meier analysis was used to estimate probabilities of overall survival. Survival curves were plotted using the Kaplan-Meier method. Cox proportional hazard regression was used to determine association of clinico-demographic factors with instantaneous hazard of mortality.

All valid data was included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

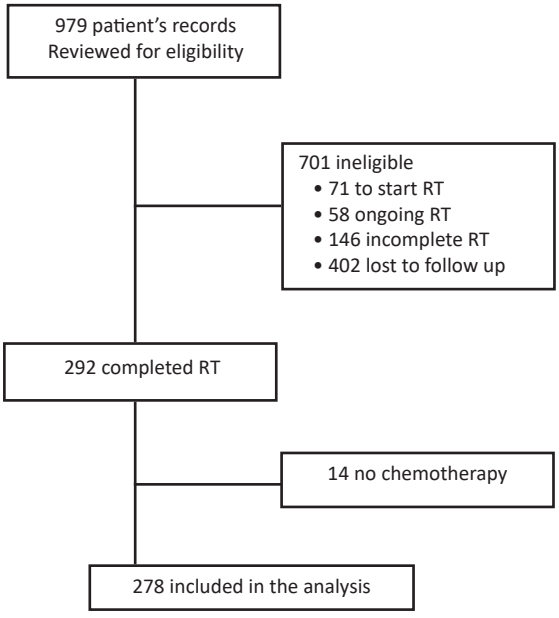


Figure 1. Inclusion and exclusion flow diagram

A total of 278 patients were included in this retrospective study, with a mean (±SD) age of 51 ± 10 years. On histopathology, 208 (75%) had squamous cell carcinoma, 56 (20%) had adenocarcinoma, and 14 (5%) had adenosquamous carcinoma. Majority of patients had FIGO stage IIIB (71%), followed by

IIB (27%). More than (58%) half of patients had largest mass dimension of 4-6 cm. Most of the patients had Cisplatin as radio sensitizer; only 3 (1%) had Carboplatin-based chemotherapy. The median durations of pelvic external beam radiotherapy or extended field radiotherapy and brachytherapy were 48 and 21 days, respectively. Profile of adenosquamous, adenocarcinoma and squamous cell carcinoma patients were comparable except for gravidity and parity (p = .012) (Table 1).

After completion of treatment, there were 189 (75.30%) patients who had complete clinical response; 20 (7.97%) had either partial clinical response (1/0.40%), stable disease (8/3.19%), or progressive disease (11/4.38%). From a median follow up of 17 months (range, 1 to 73 months), 153 (60.96%) had no evidence of disease; 42 (16.73%) had recurrent disease. The recurrence site was mostly in the cervix (60%), bone (17%), or lungs (10%). Twenty-six (9.35%) patients expired and 1 (0.36%) was lost to follow up. Of those who were dead: 6 (23.08%) had stable disease; 9 (34.62%) had disease progression; 6 (23.08%) had disease recurrence; 5 (19.23%) were unspecified. There was no significant difference in the distribution of treatment outcomes among histologic subtypes (p = .363) (Table 2).

Overall probabilities of disease free survival of locally advanced cervical cancer patients were: 99.27% (95% CI 97.12-99.82) at 6 months; 87.10% (95% CI 81.82-90.93) at 1 year; 66.52% (95% CI 58.85-73.09) at 2 years; and 52.30% (95% CI 42.69-61.03) at 3 years. The 3-year disease free survival of adenocarcinoma compared to squamous cell carcinoma and adenosquamous carcinoma was 38.8 (21.32-56.00), 56.91 (45.61-66.71), and 0.00 months at 12, 24 and 36 months respectively. For the disease free survival, squamous cell carcinoma had the highest survival probabilities at 12, 24 and 36 months. However, there was no sufficient evidence to demonstrate a difference in disease free survival curves (p=.088) (Figures 2b and 3b).

The calculated overall survival probabilities were: 99.63% (95% CI 97.43–99.75) at 6 months; 96.28% (95% CI 92.67–98.13) at 1 year; 85.58% (95% CI 78.73–90.36) at 2 years; and 82.28% (95% CI 73.76-88.26) at 3 years (Figure 2a). Survivorship functions of the three histologic types are depicted in Figure 2. All patients with adenosquamous carcinoma were alive at last follow-up except for one recorded mortality at 30 months. Compared to adenocarcinoma, squamous cell carcinoma had

Table 1. Clinico-Demographic Profile of Patients (n = 278)

	All (N = 278)	ASC (n=14)	AC (n=56)	SCC (n=208)	p-value
	Mean ± SD; Median (Range); Frequency (%)				
Age on diagnosis, Years	51.3 ± 10.5	51.36±11.84	49.61±6.91	51.81±11.19	.255*
21-29	5 (1.80)	0	0	5 (2.40)	
30-65	251 (90.29)	13 (92.86)	56 (100)	182 (87.50)	
>65	22 (7.91)	1 (7.14)	0	21 (10.10)	
Histologically proven [n=16]					**.012†**
None	12 (4.32)	3 (21.43)	3 (5.36)	6 (2.88)	
BLND	266 (95.68)	11 (78.57)	53 (94.64)	202 (97.12)	
Parity					**.012†**
P0	12 (4.32)	3 (21.43)	3 (5.36)	6 (2.88)	
≥P1	266 (95.68)	11 (78.57)	53 (94.64)	202 (97.12)	
Parity					059†
IB3	1 (0.36)	0	0	1 (0.48)	
IIA2	3 (1.08)	0	0	3 (1.44)	
IIB	74 (26.62)	5 (35.71)	23 (41.07)	46 (22.12)	
IIIA	2 (0.72)	1 (7.14)	0	1 (0.48)	
IIIB	197 (70.86)	8 (57.14)	33 (58.93)	156 (75.00)	
IIC1	1 (0.36)	0	0	1 (0.48)	
Tumor size, cm					.877†
<4	44 (15.83)	1 (7.14)	10 (17.86)	33 (15.87)	
4–6	162 (58.27)	10 (71.43)	29 (51.79)	123 (59.13)	
7–9	65 (23.38)	3 (21.43)	15 (26.79)	47 (22.60)	
≥10	7 (2.52)	0	2 (3.57)	5 (2.40)	
Chemotherapy					.802†
Cisplatin	275 (98.92)	14 (100)	55 (98.21)	206 (99.04)	
Carboplatin	3 (1.08)	0	1 (1.79)	2 (0.96)	
Number of cycles					.589*
Cisplatin	6 (1-6)	6 (4-6)	5 (2-6)	6 (1-6)	
Carboplatin	2 (1-5)	-	-	-	
Duration of PEBRT, days	48 (7-232)	48.5 (34-63)	45 (11-79)	48 (7-232)	.212*
Duration of brachytherapy, days	21 (2-330)	22 (11-49)	21 (3-330)	21 (2-205)	.723*
Number of cycles	17 (1-73)	12 (4-30)	17 (4-65)	17 (1-73)	.120*

FIGO, International Federation of Gynecology and Obsetrics; PEBRT, pelvic external beam radiation therapy.
*Statistical test: * Kruskal-Wallis test; † Fisher's Exact test*

Table 2. Treatment Outcomes of Cervical Cancer Patients (n = 278)

	All (N = 278)	ASC (n=14)	AC (n=56)	SCC (n=208)	p-value
	Frequency (%)				
Status on last follow-up					.363
Alive	251 (90.29)	13 (92.86)	48 (85.71)	191 (91.83)	
No evidence of disease	153 (60.96)	5 (38.46)	23 (47.92)	125 (65.45)	
Complete	36 (14.34)	6 (46.15)	6 (12.50)	24 (12.57)	
Partial	1 (0.40)	0	1 (2.08)	0	
Stable	8 (3.19)	0	3 (6.25)	5 (2.62)	
Progression	11 (4.38)	0	4 (8.33)	7 (3.66)	
Recurrence	42 (16.73)	2 (15.38)	11 (22.92)	29 (15.18)	
Expired	26 (9.35)	1 (7.14)	8 (14.29)	17 (8.17)	
Stable	6 (23.08)	0	1 (12.50)	5 (29.41)	
Progression	9 (34.62)	(100)	4 (50.00)	4 (23.53)	
Recurrence	6 (23.08)	0	3 (37.50)	3 (17.65)	
Unspecified	5 (19.23)	0	0	5 (29.41)	
Lost to follow-up	1 (0.36)	0	0	1 (0.48)	
Site of recurrence	[N = 48]	[N = 2]	[N = 14]	[N = 32]	-
Cervix	29 (60.42)	1 (50.00)	8 (57.14)	20 (62.50)	
Bone	8 (16.67)	0)	1 (7.14)	7 (21.88)	
Lungs	5 (10.42)	1 (50.00)	3 (21.43)	1 (3.13)	
Adrenals	1 (2.08)	0	1 (7.14)	0	
External iliac node	1 (2.08)	0	0	1 (3.13)	
Para-aortic	1 (2.08)	0	0	1 (3.13)	
Pelvic lymph node	1 (2.08)	0	1 (7.14)	0	
Periumbilical	1 (2.08)	0	0	1 (3.13)	
Vagina	1 (2.08)	0	0	1 (3.13)	

Statistical test: Chi-square test

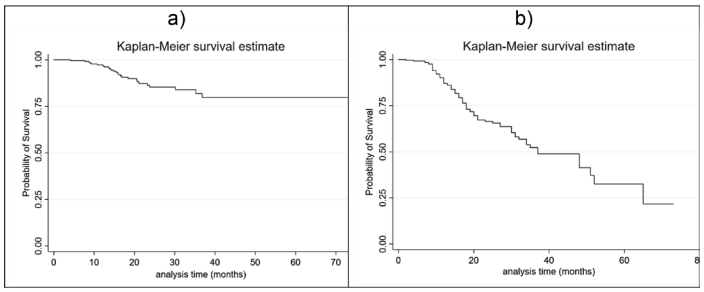


Figure 2. (a) Overall and (b) Disease Free Survival of Cervical Cancer Patients

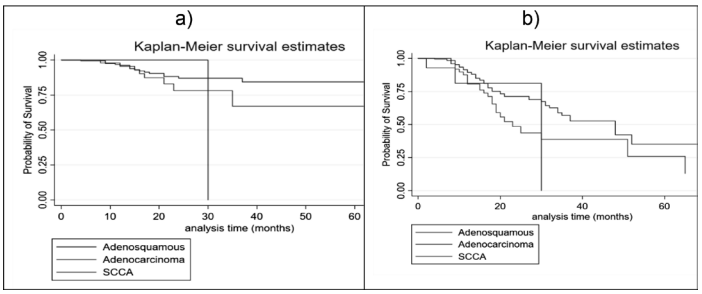


Figure 3. (a) Overall and (b) Disease Free Survival Curves, By Histologic Type of Cervical Cancer

the highest point estimate of survival probability at 12, 24, and 36 months. Differences across the three survival curves were not proven to be statistically significant (p = .197).

Analysis adjusted for age was unable to demonstrate a significant association between the clinical factors, diseases free survival and risk of mortality among all patients (Table 3 and 4).

There were 56 patients with adenocarcinoma of the cervix. Specific histologic types were endocervical (25%), endometrioid (21%), mucinous (7%), clear cell (7%), and villoglandular (5%), or unspecified (32%). In terms of grade, 16% were G1, 25% were G2, and 11% were G3 (Table 5). The most frequent sites of recurrence were cervix and lungs (Table 6).

Table 7 presents the overall survival estimates of patients with adenocarcinoma of the cervix by tumor stage, grade, and size. There was evidence that FIGO stage IIIB patients had better

Figure 3. Predictors of Disease Free Survival Among Cervical Cancer Patients

	Total	Event (N = 80)	Hazard Ratio* (95% CI)	*p*
Gravidity				
G0	12	4 (33.33)	Reference	-
≥G1	266	76 (28.68)	1.26 (0.45-3.48)	.660
Parity				
P0	12	4 (33.33)	Reference	-
≥P1	266	76 (28.68)	1.26 (0.45-3.48)	.660
FIGO stage				
IB3	1	0	-	-
IIA2	3	1 (33.33)	-	-
IIB	74	27 (36.49)	1.49 (0.93-2.38)	.099
IIIA	2	0	-	-
IIIB	197	52 (26.53)	0.64 (0.40-1.03)	.064
IIIC1	1	0	-	-
Histopathology				
Adenosquamous	14	3 (21.43)	1.14 (0.36-3.64)	.827
Adenocarcinoma	56	24 (42.86)	1.53 (0.94-2.49)	.085
Squamous cell	208	53 (25.60)	0.66 (0.41-1.06)	.083
Tumor size, cm				
<4	44	11 (25.00)	Reference	-
4–6	162	46 (28.40)	1.13 (0.58-2.19)	.728
7–9	65	23 (35.94)	1.44 (0.67-3.08)	.883
≥10	7	0	-	
Duration of PEBRT	48 (7-232)	-	1.00 (0.99-1.01)	.796
Duration of brachytherapy	21 (2-330)	-	1.00 (0.99-1.01)	.883

**Adjusted for age.*

Figure 4. Factors Associated with Risk of Mortality Among Patients (n = 278)

	Total	Death (N = 26)	Hazard Ratio* (95% CI)	*p*
Gravidity				
G0	12	1 (8.33)	Reference	-
≥G1	266	25 (9.40)	1.57 (0.21–11.59)	.660
Parity				
P0	12	1 (8.33)	Reference	-
≥P1	266	25 (9.40)	1.57 (0.21–11.59)	.660
FIGO stage				
IB3	1	0	-	-
IIA2	3	0	-	-
IIB	74	9 (12.16)	1.29 (0.57–2.91)	.538
IIIA	2	0	-	-
IIIB	197	17 (8.63)	0.78 (0.35–1.77)	.555
IIIC1	1	0	-	-
Histopathology				
Adenosquamous	14	1 (7.14)	0.90 (0.12–6.71)	.918
Adenocarcinoma	56	8 (14.29)	1.64 (0.71–3.77)	.249
Squamous cell	208	17 (8.17)	0.65 (0.29–1.46))	.300
Tumor size, cm				
<4	44	1 (2.27)	Reference	-
4–6	162	13 (8.02)	3.27 (0.43–25.19)	.255
7–9	65	12 (18.46)	7.61 (0.96–60.65)	.055
≥10	7	0	-	
Duration of PEBRT	48 (7-232)	-	1.00 (0.98–1.02)	.888
Duration of brachytherapy	21 (2-330)	-	1.00 (0.97–1.02)	.765

**Adjusted for age.*

overall survival as compared to those with stage IIB (p = .031) (Figure 3a). In contrast, survival probabilities not statistically different across tumor grades (p = .644) and sizes (p = .843) (Figures 4b and 4c).

Analysis adjusted for age was unable to demonstrate a significant association between the clinical factors and hazard of mortality among women whose primary cancer histology was adenocarcinoma (Table 8).

Figure 5. Tumor Characteristics Among Patients with Adenocarcinoma

	Frequency
Type	
Endocervical	14 (25.00)
Endometrioid	14 (25.00)
Mucinous	12 (21.43)
Clear cell	4 (7.14)
Villoglandular	4 (7.14)
Serous	3 (5.36)
Unspecified	1 (1.79)
	18 (32.14)
Tumor grade	
G1	9 (16.07)
G2	14 (25.00)
G3	6 (10.71)
Not specified	27 (48.21)

DISCUSSION

Definitive management at present for locally advanced cervical cancer is concurrent chemoradiotherapy, irrespective if it is adenocarcinoma, adenosquamous carcinoma, or squamous cell carcinoma. Impact of histological subtype to treatment outcomes in terms of overall survival and disease free survival remains a topic of consideration. Different studies give contradictory results as regards to the role of histology on cervical cancer in relation to treatment outcomes. In the present study, patients with locally advanced cervical cancer either of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma histology treated with concurrent chemoradiotherapy showed no significant difference in the treatment outcomes, overall survival and disease free survival.

In retrospect, Rose et. al. evaluated 1,671 patients included in GOG trials (No. 85, 120, 123, 165 and 191) to determine the impact of histology on cisplatin based chemoradiation in patients with locally advanced cervical cancer. Histology comprised of 89.1% squamous cell carcinoma (1,489), 6% adenosquamous (101) and 4.8% adenocarcinoma (81). Twenty-seven point five percent (27.5%) of patients with adenocarcinoma were

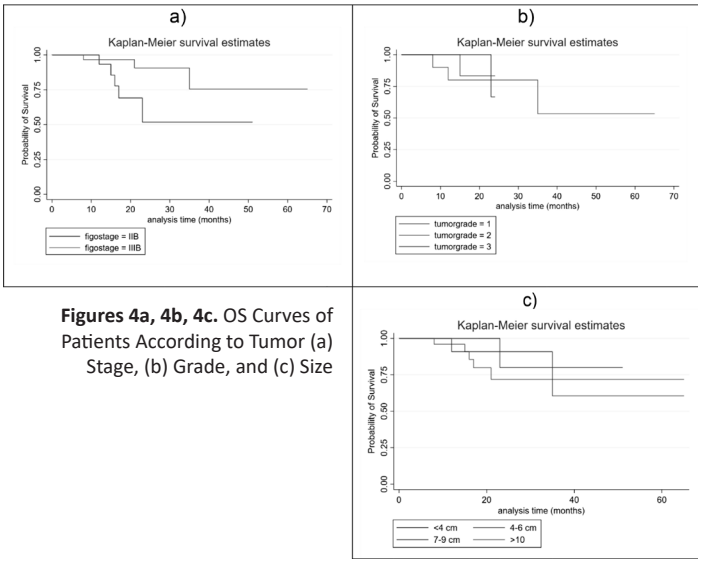
Table 6. Outcomes of patients with adenocarcinoma of the cervix (N = 56)

	Unspecified (N = 18)	Endocervical (N = 14)	Endometrioid (N = 12)	Mucinous (N = 4)	Clear Cell (N = 4)	Villoglandular (N = 3)
	Frequency (%)					
Status on last follow-up						
Alive	17 (94.44)	12 (85.71)	10 (83.33)	3 (75.00)	4 (100)	.1 (33.33)
No evidence of disease	7 (41.18)	5 (41.67)	6 (60)	125 (65.45)	2 (50)	0
Complete	3 (17.65)	0	1 (10)	1 (33.33)	1 (25)	0
Partial	1 (5.88)	0	0	0	0	0
Stable	2 (11.76)	0	0	1 (33.33)	0	0
Progression	2 (11.76)	1 (8.33)	1 (10)	0	0	1 (100)
Recurrence	2 (11.76)	6 (50)	2 (20)	0	1 (25.00)	0
Expired	1 (5.56)	2 (14.29)	2 (16.67)	1 (25)	0	2 (66.67)
Stable	0	0	0	1	0	0
Progression	1 (100)	1 (50)	1 (50)	0	0	1 (50.00)
Recurrence	0	1 (50)	1 (50)	0	0	1 (50.00)
Site of recurrence	[N = 2]	[N = 7]	[N = 3]	[N = 0]	[N = 1]	[N = 1]
Cervix	1 (50)	4 (57.14)	2 (66.67)	0	0	1 (100)
Bone	0	0	1 (33.33)	0	0	0
Lungs	0	2 (28.57)	0	0	1 (100)	0
Adrenals	0	1 (14.29)	0	0	0	0
Pelvic lymph node	1 (50)	0	0	0	0	0

Table 7. Overall survival at 12, 24, and 36 months, by tumor characteristics

	12 Months	24 Months	36 Months	p-value
	Survival Probability (95% CI)			
FIGO stage				.363
IIB	93.33 (61.26–99.03)	51.85 (15.95–79.06)	51.85 (15.95–79.06)	
IIIB	96.67 (78.61–99.52)	90.63 (65.68–97.92)	75.52 (33.04–93.13)	
Tumor grade				.644
G1	100	66.67 (5.41–94.52)	66.67 (5.41–94.52)	
G2	80.00 (40.87–94.59)	80.00 (40.87–94.59)	53.33 (8.53–85.17)	
G3	100	83.33 (27.31–97.47)	83.33 (27.31–97.47)	
Tumor size				.843
<4	100	80.00 (20.38–96.92)	80.00 (20.38–96.92)	
4–6	96.00 (74.84–99.43)	71.90 (43.59–87.72)	71.90 (43.59–87.72)	
7–9	90.91 (50.81–98.67)	90.91 (50.81–98.67)	60.61 (7.55–90.75)	

Statistical test used: Log-rank test



Figures 4a, 4b, 4c. OS Curves of Patients According to Tumor (a) Stage, (b) Grade, and (c) Size

Figure 8. Factors associated with mortality risk in adenocarcinoma subgroup (N = 56)

	Total	Death (N = 8)	Hazard Ratio* (95% CI)	*p*
FIGO stage				
IIB	23	5 (21.74)	Reference	-
IIIB	33	3 (9.09)	0.25 (0.06–1.15)	.076
Type				
Unspecified	17	0	-	-
Endocervical	14	2 (14.29)	0.69 (0.13–3.70)	.662
Endometrioid	12	2 (16.67)	1.90 (0.36–9.87)	.448
Mucinous	4	1 (25.00)	-	
Clear cell	4	0	-	-
Villoglandular	3	2 (66.67)	-	-
Serous	1	0	-	-
Tumor grade				
G1	9	1 (11.11)	Reference	-
G2	14	3 (21.43)	1.43 (0.14–14.94)	.763
G3	6	1 (16.67)	1.03 (0.06–17.31)	.986
Tumor size, cm				
<4	10	1 (10.00)	Reference	-
4–6	29	5 (17.24)	2.00 (0.23–17.62)	.531
7–9	15	2 (13.33)	1.50 (0.13–16.97)	.744
≥10	2	0	-	
Duration of PEBRT	45 (11-79)	-	1.04 (0.98–1.11)	.255
Duration of brachytherapy	21 (3-330)	-	0.95 (0.84–1.07)	.375

**Adjusted for age.*

stage Ib2, only 21.4% were stage IIIB. Clinically by internal examination, tumor size was larger in squamous cell carcinoma compared to adenocarcinoma and adenosquamous carcinoma ($p < 0.001$). Adenocarcinoma was often poorly differentiated, 46.2% of the patients. Sixty-one point five percent (61.5%) of the patients with adenocarcinoma and adenosquamous cell carcinoma underwent cisplatin based chemoradiation compared to 56.5% of squamous cell carcinoma patients. As a result, there was no difference in the progression free survival ($p = 0.315$) and overall survival ($p = 0.459$) between patients with locally advanced adenocarcinoma, adenosquamous carcinoma and squamous cell carcinoma treated with concurrent cisplatin based chemoradiation.[10] In our study, early stage cervical cancer patients were excluded. Majority of the patients' histology were squamous cell carcinoma, followed by adenocarcinoma and adenosquamous carcinoma which mostly were in FIGO stage IIIB. Difference between tumor size among the histologic subtypes were not statistically significant. However, 48% of the cervical adenocarcinoma had unspecified tumor grade. The results of this study is comparable with this retrospective study, that locally advanced adenocarcinoma or squamous cell treated with concurrent chemoradiotherapy has no significant difference in progression free survival and overall survival. In congruent to the study of Katanyoo et. al., who reviewed medical records of 423 patients with locally advanced cervical cancer; 282 patients had squamous cell carcinoma and 141 patients had adenocarcinoma. More than 50% of the patients were in stage IIB. Patients were matched with clinical stage, tumor size and treatment modalities. Adenocarcinoma had poorer complete response to treatment (RT/CCRT) compared to squamous cell carcinoma ($p = 0.004$), however, the there was no difference in 5-year overall survival rate ($p = 0.191$). Clinical stage remains the only prognostic factor that influenced overall survival.[6] The study showed only 51% of patients with adenocarcinoma response to treatment compared to 71% of patients with squamous cell carcinoma. However, it was not statistically significant in this study probably due to small sample size. Subcategorized study of adenocarcinoma in terms of the histologic types, tumor grade, tumor size and tumor stage, was unable to demonstrate a significant association between these clinical factors and hazard of mortality among women whose

primary cancer histology was adenocarcinoma.

Some investigators have proposed that adenocarcinoma and squamous cell carcinoma have distinctive genetic mutations. Wright et. al., analyzed the genomic differences between adenocarcinoma and squamous cell carcinoma of the cervix. HPV DNA was seen in 95.4% of tumors with HPV 16 present in 70.8% of the tumors and only 7.7% of HPV 18 was detected and more often in association with adenocarcinoma than in squamous cell carcinoma (15.6% vs 0%, respectively, p = 0.02). Patients with adenocarcinoma were found to be younger, married, with low grade tumor and less lymph node involvement. The most common gene mutations were in phosphatidylinositol 3-kinase (PIK3CA, 31%), Kirsten rat sarcoma (KRAS, 8.8%), and epidermal growth factor receptor (EFGR, 3.8%). Others include mutations in serine/threonine kinase 11 (STK11) gene and PTEN. Both PIK3CA mutations and PTEN loss were found in adenocarcinoma, however, in lower rates compared to squamous cell carcinoma. KRAS was only found in adenocarcinomas and EFGR only in squamous cell carcinoma.[11] Huang et. al., also stated that cervical adenocarcinoma/adenosquamous carcinoma compared to squamous cell carcinoma was more radio resistant.[12] Studies by Nakamura et. al., 2009; Kim et. al., 2004; and Oka et. al., 1996, proposed probable biologic basis for the radio resistance of cervical adenocarcinoma/adenosquamous carcinoma. One, expression of Villin 1 protein found in patients with adenocarcinoma and was linked with worse disease free survival. Two, COX-2 expression in patients with adenocarcinoma; 83% of patients with squamous cell carcinoma and 67% of patients with adenocarcinoma had complete remission after radiotherapy or chemoradiation who were COX-2 positive. Three, lower cycling cell population in adenocarcinoma.[13,14,15]

Nonetheless, some studies showed that adenocarcinoma has poorer response to treatment and overall survival. In the study of Lee et. al., comparing the survival outcomes of adenocarcinoma versus squamous cell carcinoma given before, during or after the introduction of concurrent chemoradiotherapy. A total of 80,766 patients diagnosed with cervical cancer between 1993 to 2012 were included; histology comprised of 79.9% (64,531) squamous cell carcinoma, 9.0% (7,265) adenocarcinoma, and 2.3% (1,853) adenosquamous carcinoma. Most of the patients had localized (41.6%) and regional disease (22.0%). Patient underwent either: surgery (40.9%), chemotherapy (8.6%), radiation (7.9%), chemoradiation (8.9%) or surgery plus adjuvant chemoradiation (5.8%). Squamous cell carcinoma has higher survival compared to adenocarcinoma regardless of treatment approach. For patients who underwent concurrent chemoradiotherapy specifically, still patients with adenocarcinoma has lower survival when to compared to patients with squamous cell carcinoma (p = 0.003). Adenocarcinoma was considered as an independent negative prognostic factors in the era of concurrent chemoradiotherapy. (Lee 2015).[16] Another study by Galic et. al., performed to examine the effect of histology on survival for women with invasive cervical cancer. A total of 24,562 patients with stage IB1-IVB from 1988 to 2005 were included in the study; 77% with squamous cell carcinoma, 17% with adenocarcinoma, and 6% with adenosquamous carcinoma. The study showed the influence of histology on survival of women with cervical cancer. Adenocarcinoma had poorer survival outcome for both early and advanced stage disease. The five year survival for stage IIIB carcinoma was 31.3% for squamous cell carcinoma, 20.3% for adenocarcinoma, and 24.6% for adenosquamous cell carcinomas.[5] Yokoi, et. al., reviewed the impact of histological subtype on survival in patients with locally advanced cervical cancer that were treated with definitive radiotherapy. The retrospective study included 249 patients; 90.4% with squamous cell carcinoma and 9.6% with adenocarcinoma/adenosquamous cell carcinoma. Patients with adenocarcinoma/adenosquamous cell carcinoma has significantly lower complete response ratio to treatment when compared to patients with squamous cell carcinoma (p = 0.002). Adenocarcinoma/adenosquamous cell carcinoma were more likely to developed pelvic recurrence than patients with squamous cell carcinoma, but the result was not statistically significant (p = 0.062). Adenocarcinoma/adenosquamous cell carcinoma was also associated with shorter progression free survival (p <0.001) and overall survival (p = 0.001) especially in patients who underwent concurrent chemoradiation. In addition, tumor size, advanced age and incomplete response to radiotherapy could contribute to shorter progression free survival.[17] In the study, patients with adenocarcinoma had 25% recurrence, most commonly in the cervix, followed by the lungs in comparison, 15% of the patients had recurrence, primary sites were cervix and bones.

With these contradictory studies with different results; with few studies that focused on adenocarcinoma per se and absence of a prospective study that focused solely on the treatment of adenocarcinoma, Tang et. al., conducted a prospective study that determine the efficacy and risk of new treatment approach in women with locally advanced stage cervical carcinoma by introducing neoadjuvant Cisplatin-Paclitaxel followed by concurrent chemoradiotherapy and consolidation chemotherapy with Cisplatin-Paclitaxel. The study presented that the novel treatment approach showed significant longer disease free (p<.05), cumulative survival (p<.05) and long term local tumor control (p<.05) compared to those who received concurrent chemoradiation alone which had significantly more distant metastasis and pelvic recurrence (p.<.05).[18]

Treatment response, progression free survival and overall survival is the same for women with locally advanced cervical cancer, either it is a squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma. However, further and more prospective studies concentrated to adenocarcinoma should be done, to know it uniqueness from squamous cell carcinoma thus, developing treatment strategy for cervical adenocarcinoma per se.

CONCLUSION, LIMITATION/S AND RECOMMENDATION/S

Patients with locally advanced adenocarcinoma of the cervix who underwent concurrent chemoradiation had the same treatment response and prognosis to patients with squamous cell carcinoma. The study has small number of population especially of the cervical adenocarcinoma due number of patient that was lost to follow up. Not all cervical punch biopsies were done at our institution, thus the results of pathology results were not uniformed particularly in adenocarcinoma, 51% has no tumor grade. Consequently, the researcher recommends in the future to conduct a local, prospective, multicenter research specifically targeting adenocarcinoma. ■

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Endometrial adenocarcinoma arising from adenomyosis: An unusual case

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ABSTRACT

Endometrial cancer is the third most common genital malignancy in women. It comprises 3% of cancer-related mortalities. In a woman‟s lifetime, she has a 2.8% chance of developing this malignancy. The typical precursor lesion for this is endometrial hyperplasia. Adenomyosis, on the other hand, is a benign uterine pathology that is present in up to 30% of women. There is no clear understanding on how malignant transformation occurs in this condition.

This paper presents an unusual case of a 36-year-old Gravida 1 Para 0 (0010), who consulted at the gynecologic emergency room with a chief complaint of vaginal bleeding. She was diagnosed with adenomyosis and endometrial polyps, which were also appreciated sonographically. After failed efforts to address her recurring bleeding over the course of three years, hysteroscopically and medically, she eventually underwent total hysterectomy with bilateral salpingectomy. On histopathologic examination, there were noted foci of endometrioid adenocarcinoma, FIGO grade I, confined within adenomyotic foci with no myometrial invasion. When she consulted at the Gynecologic Oncology Clinic after missing follow-ups, an impression of tumor recurrence was made based on examination and imaging. She was advised for re-exploration for bilateral oophorectomy and tumor debulking, but she opted to forego treatment. The occurrence of such malignancy with a background of a benign lesion is considered rare in literature. This emphasizes the significance of careful histopathologic evaluation, even after a surgery for a supposed benign illness.

This also poses the need for further exploration regarding the pathogenesis and clinical course of patients who have this malignant transformation.

Keywords: endometrial adenocarcinoma, adenomyosis, vaginal bleeding, pre-malignant, malignant transformation

INTRODUCTION

Endometrial cancer is the third most common genital malignancy in women, comprising 3% of cancer-related mortalities. In a woman‟s lifetime, she has a 2.8% chance of developing this malignancy.[1] The typical precursor lesion for endometrial cancer is endometrial hyperplasia.

Looking at the 2019 census of the institution where the succeeding case originated, endometrial cancer accounts for 26.8 % (239) of new malignancy cases encountered, ranking second to cervical cancer which comprises 48.7% (434) of cases. Endometrial cancer also accounts for 64.4% (125) of the operative procedures of the Division of Gynecologic Oncology of the institution, followed by cervical cancer with only 15.5% (30).[2]

Adenomyosis is characterized by the ectopic endometrial tissue, particularly from the basalis layer, inside the myometrium. Up to 60% of hysterectomy specimens in women in the late reproductive years demonstrate this finding. Studies have shown an incidence of around 30%, with more than 50% presenting with no symptoms. If present, dysmenorrhea and menorrhagia are common. Typically, adenomyosis is diagnosed incidentally by the pathologist upon histopathologic examination of the surgical specimens.[3]

This paper describes the case of a premenopausal patient with endometrial adenocarcinoma arising from adenomyosis.

CLINICAL CASE PROTOCOL

A 36-year-old Gravida 1 Para 0 (0010) consulted at the gynecologic emergency room with a chief complaint of vaginal bleeding. She has no known comorbidities or heredofamilial diseases. She is a high school graduate and works as a beauty therapist. She is a non-smoker and has occasional alcoholic beverage intake, but denies illicit drug use. She is slightly overweight with a BMI of 23.9. She had her first coitus at 28 years old with one lifetime sexual partner who has been her common law partner. She had her menarche at 14 years old, with regular monthly intervals occurring between 28 to 30 days, lasting 7 days, using up to 5 moderately-soaked pads per day, and with associated dysmenorrhea.

The patient‟s only pregnancy was last 2013 which turned out to be a molar pregnancy, for which she underwent suction curettage and post-surgical methotrexate prophylaxis at another local hospital. She is desirous of pregnancy.

She had two hospitalizations in a span of three years for vaginal bleeding. The impression for her was abnormal uterine bleeding secondary to adenomyosis and endometrial polyp. She underwent blood transfusions for her anemia. During the first admission, she underwent hysteroscopic polypectomy, revealing an endometrial polyp with no evidence of malignancy seen. She

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Finalist, SGOP 2020 Interesting Case Contest

Poster Presentation, International Gynecologic Cancer Society 2020 Global Meeting (virtual)

Financial Disclosure:
The authors did not report any potential conflicts of interest.

was advised GnRH injections every 28 days for 3 months, and she was then lost to follow-up. During her second admission, she underwent diagnostic hysteroscopy, which revealed the endometrium was generally thin with no distinct masses. She was advised GnRH injections every 28 days for 3 months. She was able to complete two months of therapy but her heavy vaginal bleeding recurred, prompting consult at the emergency room. On internal examination, the cervix was 2.5 x 2.5 cm and was smooth, with a corpus enlarged to 22 weeks size. There were no adnexal masses palpated. Transvaginal ultrasound revealed an enlarged uterus with sonographic findings suggestive of adenomyosis, endometrial mass (heterogenous mass 4.1 x 1.8 x 1.2 cm) consider endometrial pathology and normal ovaries (Figure 1). Pap smear was negative for malignancy. After her anemia was corrected, she underwent total hysterectomy and bilateral salpingectomy.

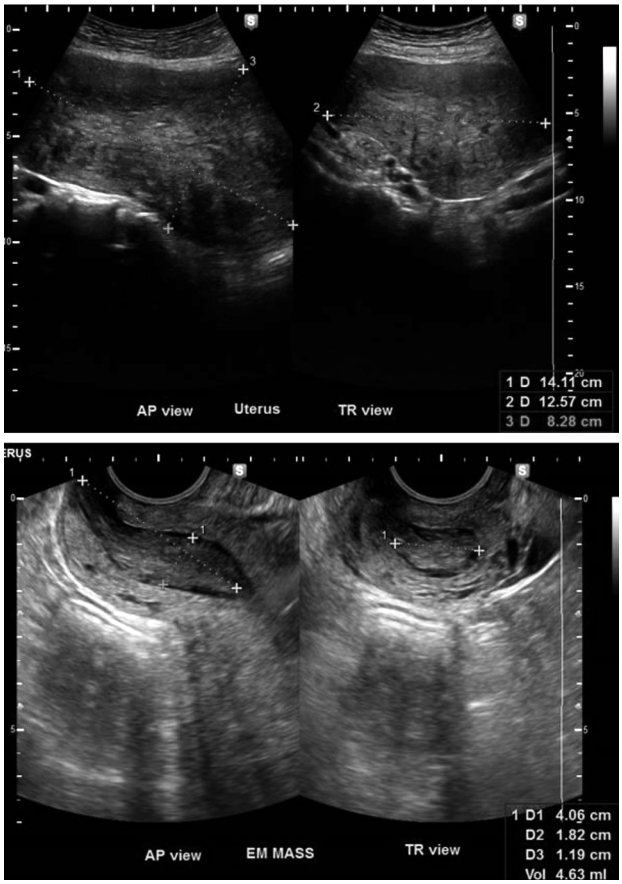

Figure 1. Transvaginal ultrasound A. Anteroposterior (AP) and transverse (TR) views of the uterus. B. Anteroposterior (AP) and transverse (TR) views of endometrial mass

Intraoperatively, there was no ascites. The liver, subdiaphragmatic surface, spleen, stomach, kidneys, omentum and intestinal surfaces were smooth and grossly normal on inspection and palpation. There were no palpable para-aortic and pelvic nodes. The uterus measured 15 x 17 x 7.5 cm with a tan and smooth serosal surface (Figure 2). The cervix measured 1.5 x 1.5 x 2.5 cm and appeared grossly normal. On cut section, the uterus was filled with blood clots with aggregated diameter of 10 x 10 x 3 cm. The myometrium measured 4.0 cm anteriorly and 3.5 cm posteriorly. The endometrium was spongy and thin at 0.2 cm. The uterine cavity measured 12 cm, 2.5 cm of which was the

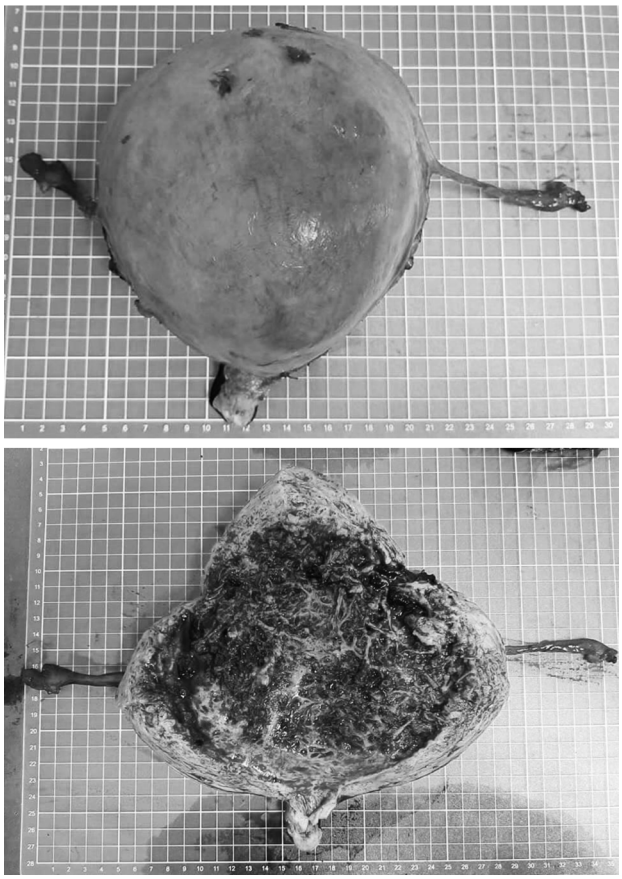

Figure 2. Gross specimen. A. Uncut uterus. B. Cut section of the uterus. The endometrial cavity was previously occupied by blood clots and these were removed prior to taking the picture. There were no masses appreciated

endocervical canal. The right fallopian tube measured 15.0 x 0.5 cm, while the left fallopian tube measured 15.0 x 0.6 cm. Both of which were grossly normal. The surgery was unremarkable and the estimated blood loss was 300 cc.

Histopathology revealed multiple foci of endometrioid adenocarcinoma, FIGO grade I, confined within adenomyotic foci with no myometrial invasion. No definite lympho-ascular space invasion was seen. The cervical resection margin was negative for tumor. Other findings included multiple endometrial polyps and acute on chronic cervicitis and squamous metaplasia. No diagnostic abnormality was recognized on bilateral fallopian tubes.

One month post-operatively, she consulted the Gynecologic Oncology Clinic. She was stable with no abdominal pain or vaginal bleeding. On internal examination, she has a smooth vagina, intact stump and the bilateral paracolpia were smooth and pliable. She was advised chest X-ray and abdominopelvic CT scan, but she was again lost to follow-up. Three months post-operatively, she consulted again at the clinic. At this time, she was still stable and asymptomatic. However, on internal examination, there was a 2.0 x 1.0 cm nodular mass at the right superoanterior portion of the vaginal stump (Figure 3). No pelvic masses were appreciated. Her chest X-ray was unremarkable but her abdominopelvic CT scan revealed a minimally-enhancing focus at the left adnexa measuring 1.4 x 2.4 x 2.2 cm and two similar foci at the presacral area measuring 2.2 x 2.4 x 1.4 cm and 2.2 x 1.3 x 1.5 cm, for which tumoral seeding or recurrence is not ruled out. Apart from the aforementioned lesions, fatty infiltration of

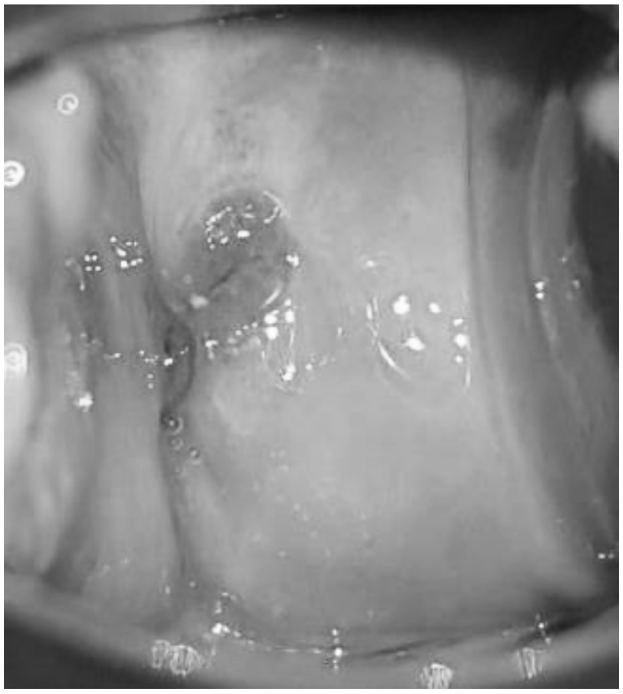

Figure 3. Vaginal stump mass

the liver and simple hepatic and renal cortical cysts were seen. A biopsy was done from the vaginal stump mass and histopathology revealed vaginal tissue with adenosis, metaplasia and acute inflammation. No malignancy present. The plan at that time was for re-exploratory laparotomy, bilateral salpingooophorectomy, bilateral pelvic lymph node dissection, paraaortic lymph node sampling, infracolic omentectomy, random peritoneal biopsy, tumor debulking and upper vaginectomy. The patient was again lost to follow-up. Four months post-operatively, upon attempting to reach out to the patient, she verbalized that she is asymptomatic, but she already went home to the province and decided not to pursue any adjuvant treatment.

CASE DISCUSSION

The reproductive and menopausal years are the peak periods for the occurrence of endometrial adenocarcinoma with 63-years-old being the mean age of incidence and most patients between 50 and 59 years old. Most cases are sporadic but hereditary endometrial cancer has been identified in association

with hereditary nonpolyposis colon cancer (HNPCC), with up to 30 – 61% lifetime risk for those who have the latter.[4]

For adenomyosis, multiple risk factors include obesity, nulliparity, late menopause and history of unopposed estrogen use, while protective factors include elevated intake of most vegetables, fresh fruits, whole grain bread, and pasta and use of oral contraceptives.[4] There are some case reports associating adenomyosis in a Mayer-Rokitansky-Kuster-Hauser Syndrome.[5,6,7,8] In the case, the patient did not seem to have risk factors aside from her being slightlyoverweight. Also, based on her clinical presentation, she did not have Mayer-Rokitansky-Kuster-Hauser Syndrome.

The pathogenesis of adenomyosis is unknown. Still, the disruption of the endometrial-myometrial barrier is thought to be associated with the condition. This disruption can occur in histories of dilatation and curettage or any prior uterine surgery.3 The patient in the case report had a previous history of suction curettage for her molar pregnancy.

Leyendecker et al (2009) described how adenomyosis can occur spontaneously even without a prior uterine procedure through the activation of the "tissue injury and repair" (TIAR) mechanism. In the spontaneously developing disease, microtraumatizations from chronic uterine peristaltic activity or phases of hyperperistalsis consequently induce the activation of the mechanism of "tissue injury and repair‟ (TIAR), resulting to local production of estrogen. Because the peristaltic activity continues, the injured sites could increase, also continuing estrogen release. The estrogen then takes over in a paracrine manner over the ovarian control over the peristaltic activity of the uterus. This results to perrmanent hyperperistalsis and self-perpetuation of the process. Eventually, the overt auto-traumatization disclocates portions of the basal endometrium into the myometrial walls.[9]

Estrogen has a key role in adenomyosis. It is known that estradiol levels are found out to be increased in the menstrual blood of women with adenomyosis. Adenomyotic tissues also show increased expression of P450 aromatase.[10] Garavaglia et al (2015) stated that there is also increased expression of estradiol receptor (ER) expression compared to the normal endometrium. Throughout the menstrual cycle, there is also an expression of the apoptosis-suppressing gene product, Bcl-2. The Bcl-2 and ER co-expression, along with the hyper-estrogenic metabolic states may facilitate not only the invagination process but also the infiltration of the adenomyosis into the myometrium. Hyperestrogenism also stimulates the production of IL 10, a major anti-inflammatory cytokine. This then aids in the development and continuation of immunosuppression. Hence, the ectopic foci within the myometrium persists without elimination by the immune system of the host.[11] We now see how adenomyosis, just like endometrial adenocarcinoma, is closely linked to hyperstrogenism.

Two months prior to the patient‟s hysterectomy, she underwent diagnostic hysteroscopy, revealing a thin endometrium. Hence, no biopsy was done. A positive hysteroscopy result was associated with a 72% probability of endometrial cancer, but a negative result reduced this probability to 0.6%. The corresponding probabilities for endometrial disease were 55% with a positive result and 3% with a negative result.[4] Before and during the surgery, there was no suspicion of malignancy. The histopathology revealing multiple foci of endometrioid adenocarcinoma, FIGO grade I, confined within adenomyotic foci with no myometrial invasion was then unexpected. Since foci of adenocarcinoma were found in the areas of adenomyosis, the tissue harboring the malignancy would not be found or located in the endometrium, but within the myometrium.

In 1959, Colman and Rosenthal proposed three criteria to be met to diagnose cancer arising within adenomyosis: (1) The cancer must be absent from a normal surrounding endometrium; (2) The cancer must be seen to arise from the adenomyotic epithelium without invasion from another source; and (3) Endometrial stromal cells must be present in order to support the diagnosis of adenomyosis. However, the above criteria, which the patient presented actually fulfilled, were not universally adopted.[12]

How is endometrial adenocarcinoma arising from adenomyosis staged? Jacques et al in 1990 and Hanley et al in 2010 stated that the tumor is not myoinvasive if there is no

myometrial invasion outside the adenomyotic lesions. Even if the adenomyosis is present in the outer half of the myometrium, but there is no invasion outside of the lesions, the tumor is considered a FIGO stage 1A. The prognostic significance of the involvement of adenomyosis, especially in the outer half of the myometrium, has been poorly studied. Nonetheless, current data support that this has no or little adverse significance in the prognosis of endometrioid adenocarcinomas.[13,14]

Endometrial adenocarcinoma arising from adenomyosis is rare.[1,15,16] A study by Zouzulas in 2018 that correlated adenomyosis and endometrial cancer in a span of six years showed that out of 229 cases of endometrial cancer, 28% (64) had concurrently endometrial cancer and adenomyosis. In these 64 patients, 11% (8) had malignant transformation of adenomyosis.[17] In the largest review in literature concerning adenomyosis and endometrial cancer by Habiba et al in 2018, they identified 78 case reports in 68 articles describing a case of adenocarcinoma arising from adenomyotic foci. They also concluded that estimating the exact prevalence is challenging because of the lack of large case-series.[12] An old study in 1980 by Hernandez and Woodruff noted eight cases at The Johns Hopkins Hospital between the years 1955 and 1974, with the youngest patient aged 38 years old and the second youngest aged 54-years-old. The adenocarcinoma in adenomyosis was well differentiated in all cases. Myometrial involvement was present to a depth of less than 50% in half of the cases.[18] In 2018, Antovska et al reported a case of endometrioid adenocarcinoma arising in adenomyoma in a woman with a genital prolapse without other clinical symptoms. Just as in our patient, there was also no infiltration of the surrounding myometrium and no lymphovascular invasion.[1] The aforementioned studies point to a less aggressive behaviour, which is similar to the case presented. Woodruff et al in 1986 also presented two cases of adenocarcinoma arising from adenomyosis. There were no surface endometrial changes. Total hysterectomy with bilateral adnexectomy was performed on these two postmenopausal women due to their having persistent atypical cytology, even if they had negative findings on biopsies from curettage. It was only after histopathologic examination of the surgical specimens that the diagnosis of endometrial adenocarcinoma was made.16 Going back to the study by Zouzulas in 2018, the 11% who had malignant transformation of adenomyosis to endometrial adenocarcinoma had a mean age of 65-years-old with no premenopausal case. In addition, majority of them had stage I cancer. As for the tumor grade, majority was grade II (42.8%), followed by grade I (28.6%) and by grade III 28.6%).[17] This is somewhat congruent to our case which had less aggressive grading and spread. Reviewing the study by Habiba et al in 2018, they concluded that better prognosis for adenomyosis-associated endometrial cancer is accepted nowadays, but this may be a factor of the early stage at which it is detected.[12] Sasaki et al in 2001 reported adenocarcinoma arising in adenomyosis without endometrial involvement in a 53-year-old. However, there were already lymph node metastases and serous uterine involvement by the time of the diagnosis. Even if the eutopic endometrium did not show malignancy, the uterine fundus tumor was composed mostly of adenocarcinoma with stromal invasion. Around the carcinoma, there were multiple adenomyotic foci. Some of those exhibited transition to adenocarcinoma. There was no peritoneal dissemination.[19] This is in contrast to the case since the patient was post-menopausal, the diagnosis of malignancy was made prior to the surgery from smear cytology of the endometrium revealing adenocarcinoma and that there was already advanced disease at the time of diagnosis. In 2015, Nishida et al reported a 36-year-old with a four year history of adenomyosis, who presented with multiple tumors in the myometrium, omentum, liver and bone on imaging. Endometrial biopsy was negative for malignancy. The initial impression was a uterine sarcoma. On histopathologic examination, however, grade 3 endometrioid adenocarcinoma with squamous differentiation was revealed. The endometrium demonstrated no malignancy, but cancer nests adjacent to the adenomyotic foci were seen. The researchers diagnosed this as a case of adenocarcinoma originating from adenomyosis. The patient rejected adjuvant therapy and died 16 days later from rapid enlargement and rupture of the metastasized liver and respiratory failure.[20] This is again in contrast to the case presented such that advanced disease was already present at the time of the diagnosis. Other studies aforementioned did not look into the course of this subset of patients post-operatively but the patient of Nishida et al demonstrated the aggressive nature of the malignancy leading to her death a little more than two weeks after the surgery. The case presented did not result to death, but tumor recurrence was determined after 90 days of surgery. The limitation for the case presented, though, was that the patient had poor follow-up post-operatively which decreased the opportunity for earlier detection of the recurrence. In conclusion, endometrial adenocarcinoma arising from adenomyosis is truly unusual. Cases like this are determined only post-operatively during examination of the surgical specimen. The absence of malignancy in the endometrium which could be accessed through hysteroscopy, curettage and biopsy causes the delay in the diagnosis. This case highlights the rare possibility of malignancy from a supposedly benign lesion, emphasizing the need for a thorough histopathologic examination even for specimens removed for benign reasons and even in pre-menopausal patients. In future studies, it is noteworthy to explore further the pathogenesis of this kind of tumor. How indeed does malignant transformation occur in the ectopic endometrial tissue of adenomyosis? In addition, it is also recommended to investigate the post-operative clinical course of the patients who had such histopathologic findings. Do cases like this proceed to be more aggressive or less aggressive? Clinicians need to understand the nature and predict the behaviour of this malignancy with a rather atypical evolution to be able to render more optimal care to their patients. ■

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Radical vaginal hysterectomy with bilateral salpingo-oophorectomy, extraperitoneal bilateral pelvic lymph node dissection: Surgical approach to cervical cancer associated with pelvic organ prolapse

Keno Lorenzo D. Ong, MD; Maria Constancia Y. Wylengco, MD, FPOGS, FSGOP, FPSCPC and Jericho Thaddeus P. Luna, MD, FPOGS, FSGOP, FPSCPC

ABSTRACT

Pelvic organ prolapse is a common clinical entity with roughly 13% of women undergoing surgery for prolapse during their lifetime[10]. The coexistence of cervical cancer and pelvic organ prolapse is an extremely rare condition. The available data on literature suggests the incidence to be between 0.14%-1%[2]. This paper describes a case of early stage squamous cell carcinoma, associated with pelvic organ prolapse. A surgical approach, vaginal radical hysterectomy with bilateral salpingo-oophorectomy was used for this case. Currently, there is no standard of treatment for cervical cancer associated with pelvic organ prolapse. There are no available data that shows that one treatment approach is superior to the other due to the rarity of the condition.

Keywords: Cervical cancer, Pelvic organ prolapse, radical vagina hysterectomy, extraperitoneal bilateral pelvic lymph node dissection.

INTRODUCTION

Cervical Cancer is the 2nd leading cancer site among women in the Philippines. An estimated 7,277 new cases and 3,807 deaths due to, cervical cancer are expected to occur every year[9]. Pelvic organ prolapse is a common clinical entity with roughly 13% of women undergoing surgery for prolapse during their lifetime[10]. The coexistence of cervical cancer and pelvic organ prolapse is an extremely rare condition. The available data on literature suggests the incidence to be between 0.14%-1%[2]. Definitive treatment for cervical cancer depends on the stage of the disease. Treatment options are surgery, chemotherapy, radiation and or a combination of each. Currently, there is no standard of treatment for cervical cancer associated with pelvic organ prolapse. Some speculate that surgical treatment has more benefit than concurrent chemoradiation and others argue the reverse[2]. There are no available data that shows that one treatment approach is superior to the other due to the rarity of the condition.

This paper describes a case of early stage squamous cell carcinoma, associated with pelvic organ prolapse. A surgical approach, vaginal radical hysterectomy with bilateral salpingo-oophorectomy, first described by the surgeon Anton Pawlik and was popularized the Austrian surgeon Frederik Schauta who used the procedure for patients with cervical cancer[3]. An extraperitoneal approach was done for the pelvic lymph node dissection.

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Financial Disclosure:
The authors did not report any potential conflicts of interest

CASE REPORT

ES, a 64 year-old, Gravida 10 Para 9 (9015), Filipino consulted with a chief complaint an introital mass.[10] years prior to admission, she noted a reducible introital bulge, more pronounced when standing and walking with no other associated symptoms. In the interim, there was gradual enlargement of the introital mass. 8 months prior to admission, the introital mass was now non-reducible and accompanied by urinary frequency, sensation of incomplete bladder emptying, urinary incontinence and nocturia. There were no bowel movement changes or vaginal bleeding. She then sought consult at our institution with an assessment of Pelvic organ prolapse stage IV. She was referred to the service of Urogynecology and the operative plan was to do vaginal hysterectomy, anterior and posterior colporrhaphy, McCall culdoplasty, bilateral iliococcygeal fixation. Patient was then lost to follow-up. 1 month prior to admission, patient went back for follow-up. At this time, on examination, the vagina is pale, no lesions, the cervix measures 4 x 2 cms with note of erosions. Assessment at this time was a suspicious cervix (Figure 1). A cervical punch biopsy was done with a histopathologic diagnosis of stratified squamous epithelium-lined mucosa with atypical proliferative, acute inflammation and focus suspicious for invasion. With the high suspicion for a malignant process, a colposcopy-guided biopsy was done. On colposcopy, The squamocolumnar junction was not visible, no atypical vessels, there was dense acetowhitening at the 7-9 o'clock position with a sharp and well demarcated border (Figure 2). The cervical os cannot be visualized and there was no Lugol's uptake (Figure 3). Punch biopsy specimens were taken from the suspicious areas of the cervix (Figure 4). On histopathology, it showed squamous cell carcinoma, arising from a high grade squamous intraepithelial lesion. On pelvic MRI with contrast there is a fairly-defined, T1W-isointense, T2W-hypointense (to muscle), homogeneously enhancing focus with restricted water diffusion at the cervix

measuring 1.4 x 2.7 x 3.4 cm (Figure 5). She was then scheduled to undergo extraperitoneal bilateral pelvic lymph node dissection, vaginal radical hysterectomy, bilateral salpingo-oophorectomy, McCall culdoplasty with anterior and posterior colporrhaphy.

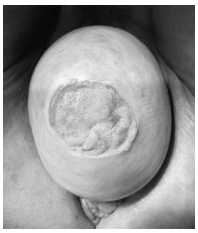

Figure 1. Patient's suspicious cervix

Figure 2. Post ascetic acid application. Dense acetowhitening at the 7-9 o'clock position with a sharp and well demarcated border

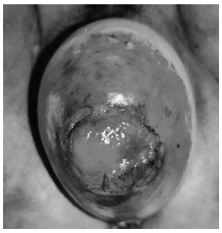

Figure 3. Post application of Lugol's solution. No Lugol's uptakvix

Figure 4. Areas where biopsy specimens were taken

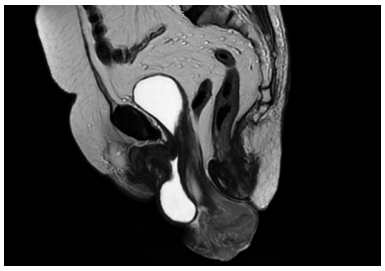

Figure 5. Fairly-defined, T1W-isointense, T2W-hypointense (to muscle), homogeneously enhancing focus with restricted water diffusion at the cervix measuring 1.4 x 2.7 x 3.4 cm

Gross specimen

The cervix measured 3.5 x 3.0 x 3.0 cm, with the posterior cervical lip converted into a 2.5 x 3.5 x 3.0 cm fungating mass with more than 1/3 cervical stromal invasion at the 4-9 o'clock position. The vaginal cuff was 2.0 cm at its shortest length laterally, while the longest vaginal cuff was 2.5 cm anteriorly and posteriorly. Both parametria were 2.5 x 3.0 cm, grossly free of tumor. On cut section, the uterine canal measured 8.0 cm, 3.0 cm of which was the endocervical canal. The myometrium measured 1 cm anteriorly and posteriorly. The endometrium was tan, smooth, and thin measuring 0.4 cm. The right ovary was 3 x 0. 8 x 0.5 cm, while the right fallopian tube was 8.5 x 0.5 cm. The left ovary was 2.5 x 0.8 x 0.5 cm, the left fallopian tube was 8.0 x 0.5 cm. Both were grossly normal. The harvested pelvic lymph nodes were not suspicious for malignancy.

Histopathology of the surgical specimen

Final histopathology result showed Squamous cell carcinoma, non-keratinizing, moderately-differentiated, 3 centimeters in greatest tumor width, involving the 4 o'clock to 8 o'clock position of the uterine cervix. Tumor invades the middle third of the cervical stroma (0.8 cm of 1.3 cm) no definite lymphovascular space and perineural invasion identified. Final diagnosis is Squamous cell carcinoma, non-keratinizing, cervix, stage IB2 (Figures 6A and 6B).

The planned adjuvant treatment is pelvic EBRT concurrent with weekly Cisplatin (40 mg/m2). Unfortunately the patient was again lost to follow-up. As of writing this paper, the patient has followed up. On repeat pelvic examination and imaging the patient has no evidence of disease for 1 year.

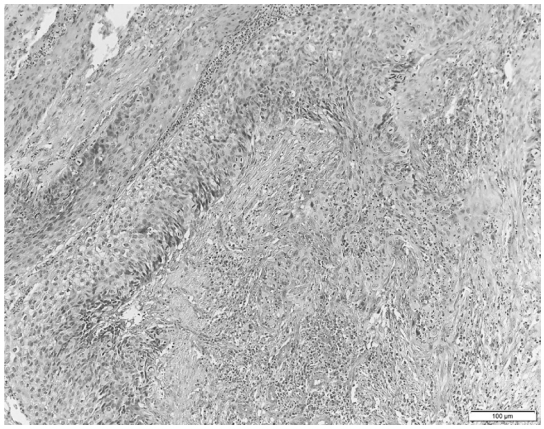

Figure 6A. Stratified squamous epithelial lining with the lower two-third portion showing nuclear atypia (hyperchromatic, irregular nuclear membrane, prominent nucleoli, and multiple mitoses) and disordered arrangement – HSIL. There is also a focus of invasion where we see disruption of the basement membrane and we see the neoplastic squamoid cells now invading into the stroma

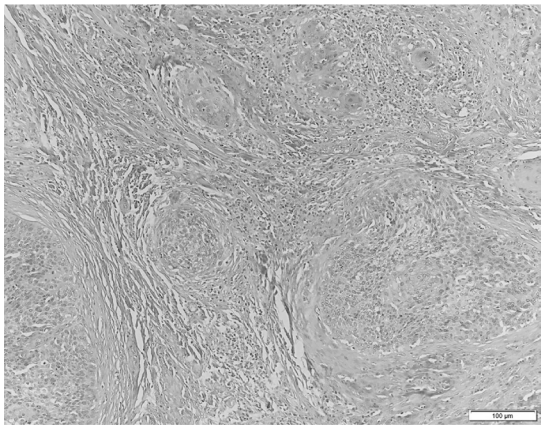

Figure 6B. The same features are seen in the definitive specimen. Here we see islands/nests and occasional individual neoplastic squamoid cells invading the stroma with noted prominent stromal desmoplastic reaction

DISCUSSION

Cervical cancer associated with pelvic organ prolapse is a rare condition with no recommended standard of treatment. Most cases in literature suggest a radical vaginal hysterectomy with bilateral pelvic lymphadenectomy, external pelvic radiation and chemotherapy[1]. The management for the condition varies widely. Most common treatment modality is surgery (57.1%) and pelvic radiotherapy (71.4%)[1]. Based on literature, whenever possible surgery should be the treatment approach of choice because radiation therapy might predispose to serious injuries of the other prolapsed viscera[6]. Based on the study by Matsuo et al, Surgery-based treatment was associated with marginally but significantly better recurrence-free survival than radiation-based treatment: 5-year rate 72.0 % and 62.9 %, respectively. Surgery-based treatment was associated with significantly better disease-specific overall survival than radiation- based treatment: 5-year rate 77.0 % and 68.2 %, respectively[2].

Vaginal radical hysterectomy for the surgical treatment of cervical cancer was first described by Schauta[4]. During that time, abdominal radical hysterectomy, pioneered by Wertheim, was the surgical treatment for cervical cancer, but with high operative mortality rates[4]. In the 1950s, because of the high complication rate of ARH, Mitra[4] described a combined extra-peritoneal pelvic lymph-node dissection and a vaginal radical hysterectomy[4]. Our institution the Philippine General Hospital Division of Gynecologic Oncology has it's own Eligibility Criteria for radical vaginal hysterectomy; selected IB2-IIA1 and Stage IB1-IIA1 with pelvic organ prolapse. Today, with the availability of laparoscopy, a combined laparoscopic pelvic lymph node dissection and radical vaginal hysterectomy, is a surgical approach option.

The extraperitoneal lymphadenectomy approach may be the most cost-effective and readily available option for surgically managing these patients since it has a shorter operating time, shorter learning curve than laparoscopy and additionally minimal requirements for surgical instruments[7]. In a study by Lapricete et al., comparing extraperitoneal and laparoscopic pelvic lymphadenectomy, the median time to perform a radical vaginal hysterectomy and bilateral salpingo-oophorectomy was 65 (44-166) minutes. In patients who had undergone a laparoscopic or an extraperitoneal dissection, the median number of pelvic lymph nodes that were identified were 18 (7–28) and 32 (16– 42) ($p < 0.05$), respectively[7]. The median time required to complete lymphadenectomies using the laparoscopic procedures was significantly higher than for the extraperitoneal route [68 (42–92) versus 48 (36–64) min, $p < 0.05$]7 and the intraoperative blood loss was similar between the two groups[7]. The patient discussed in this paper underwent extraperitoneal lymph node dissection, radical vaginal salpingo-oophorectomy, McCall culdoplasty with anterior and posterior colporrhaphy. The prolapse procedure will not be included in the description of the surgical technique.

Surgical Technique

The patient is placed in dorsal lithotomy position. Extraperitoneal pelvic lymph node dissection done by making a curvilinear incision at the suprapubic area, 2 cm above the superior border of the pubic symphysis, medial to the anterior superior iliac spine, following the iliac crest and extending cephalad until 2 cm above the anterior superior iliac spines (Figure 7). The incision is then carried down until the fascial layer. The peritoneum and visceral contents are then separated from the overlying fascia using careful blunt dissection. The external iliac vessels are then identified, the ureter is identified along the medial peritoneal sheath and retracted away from the iliac vessels (Figure 8). The perivascular tissue and lymph nodes are then carefully dissected from the perivascular sheath of the external and internal iliac vessel and obturator fossa (Figure 9). The uterine artery is then ligated to its origin at the hypogastric artery. The ovarian vessels were then identified superior to the ureters and grasped with Babcock clamps (Figure 10). This was triply clamped with Mixters, cut and suture ligated. After hemostasis, the abdominal incisions are then closed in layers.

Radical vaginal hysterectomy with bilateral salpingo-oophorectomy is done by grasping the anterior and posterior lips of the cervix with Allis forceps and pulling down gently. A circumferential incision was done on the cervix, 3 cm away from the most distal edge of the tumor (Figure 11). Allis clamps were then used to appose the anterior and posterior vaginal edges over the cervical mass. Mobilization of the vaginal wall off the pubocervical fascia was done by careful sharp and blunt dissection. Peritoneum of the cul de sac was opened; uterus and bilateral adnexae were palpated. Pre-sacral and both pararectal spaces were opened at the 4-5 o'clock and 6-7 o'clock positions by blunt dissection. The Uterosacral ligaments were clamped and ligated as close to the sacrum as possible (Figure 12). The uterine fundus was grasped and deflected posteriorly with the non-dominant hand through the cul de sac opening, and used to develop the prevesical space. Both paravesical spaces were developed at the 2-3 o'clock and 10-11 o'clock positions using blunt dissection. The ureter was identified and isolated using Babcock clamps (Figure 13). Bladder pillars doubly-clamped, cut and suture ligated. Bladder deflected superiorly using a Deaver retractor. Cardinal ligaments were exposed by pulling the cervix and uterine fundus to the contralateral side, then clamped and suture-ligated as close to the pelvic side walls as possible (Figure 14). Both adnexa were exposed by pulling the uterine corpus to the contralateral side, and both infundibulopelvic ligaments were again triply clamped, cut and suture ligated (Figure 15).

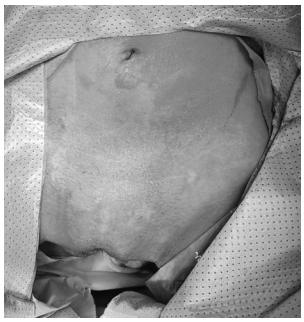

Figure 7

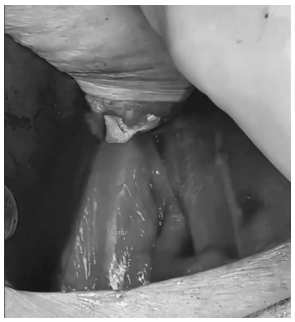

Figure 8. Ureter identified along the medial peritoneal sheath

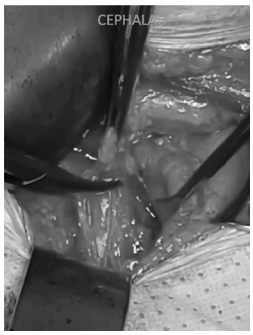

Figure 9. Perivascular tissue and lymph nodes dissected from the perivascular sheath of the external and internal iliac vessel and obturator fossa

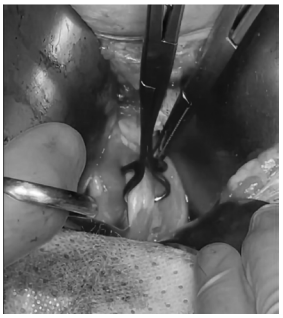

Figure 10. Ovarian vessels

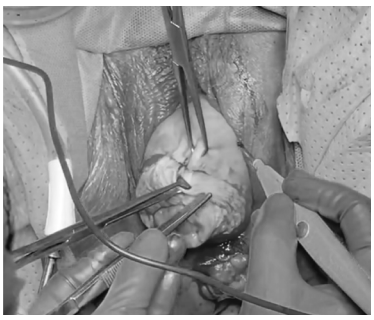

Figure 11. Circumferential incision on the cervix, 3 cm away from the most distal edge of the tumor

Figure 12. Tagged uterosacral ligament

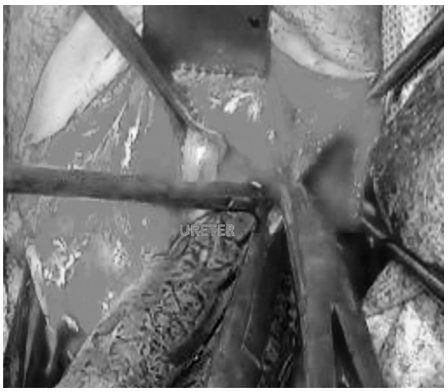

Figure 13. Ureter identified and deflected during clamping of the bladder pillar

Figure 14. Ligated and tagged cardinal ligament

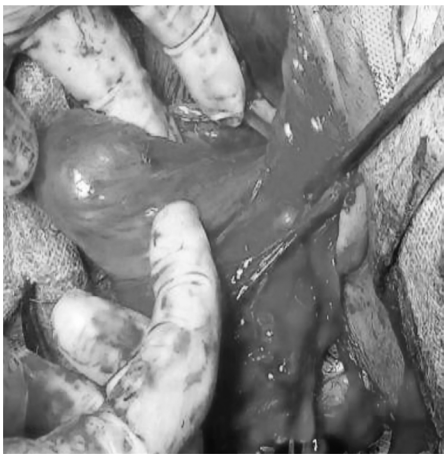

Figure 15. Ligation of the infindibulopelvic ligament

SUMMARY

Cervical cancer associated with pelvic organ prolapse is a rare clinical entity with no established treatment guidelines. Options for treatment include surgery, chemotherapy, radiation or a combination of each depending on the stage of the disease. Radical vaginal hysterectomy with bilateral salpingo-oophorectomy, extraperitoneal bilateral pelvic node dissection is an option for early stage disease. The extraperitoneal approach to pelvic lymph node dissection may be a good approach for low-resource settings or when there is unavailability of the machine and or experienced laparoscopist. This surgical procedure may be technically difficult for an inexperienced surgeon but can be done safely by an experienced pelvic surgeon with no intraoperative or post-operative complications. ■

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Intraperitoneal/intravenous chemotherapy following neoadjuvant chemotherapy and interval debulking surgery in advanced stage epithelial ovarian cancer

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ABSTRACT

The role of intraperitoneal port chemotherapy (IP) in treating newly diagnosed advanced-stage epithelial ovarian cancer (EOC) has been the subject of controversy for many decades. Although adjuvant intraperitoneal chemotherapy (IP) demonstrated improvements in the survival of patients who underwent upfront surgery, tolerance and administration have proven challenging and have not been widely accepted as a standard treatment because of fear of toxicity. Traditionally, intraperitoneal/intravenous (IP/IV) chemotherapy is indicated in EOC patients who had undergone optimal primary debulking surgery, and currently, there are limited studies that determine the efficacy of (IP/IV) chemotherapy following neoadjuvant chemotherapy combined with interval debulking surgery.

This is a case of 60 years old, G1P1 (1001) with advanced-stage epithelial ovarian carcinoma with a poor histologic variant known to be platinum-based chemo-resistant in the literature, who received a unique approach to IP/IV chemotherapy. She presented with bloatedness and gradual abdominal enlargement. She underwent exploratory laparotomy, peritoneal fluid cytology, adhesiolysis, and biopsy of the left ovarian mass in a secondary hospital. The planned upfront surgery has not resulted in optimal cytoreduction hence patient was referred to our institution for definitive treatment. On clinical examination coupled with an imaging study, the mass was unresectable hence she was given neoadjuvant chemotherapy with carboplatin and paclitaxel for 5 cycles and eventually underwent interval debulking surgery (IDS). During the IDS, there was complete resection of the disease hence the decision to insert an intraperitoneal port was made. She had adjuvant intraperitoneal/intravenous chemotherapy for three cycles using the same regimen which resulted in a complete response of the disease.

Keywords: *Clear Cell Carcinoma, Intraperitoneal/Intravenous chemotherapy, Neoadjuvant Chemotherapy, Interval Debulking Surgery*

INTRODUCTION

Ovarian cancer is one of the most common gynecologic cancers, with 313,959 new cases and 207,252 deaths reported worldwide in 2020.[1] This accounted for more deaths than any other cancer of the female reproductive tract. In the Philippines, it ranks as the second most frequent gynecologic cancer and the second most common cancer death[2], and approximately 75% of women presented with advanced disease upon diagnosis.[3]

In epithelial ovarian cancer patients, the peritoneal cavity is the primary site of spread and recurrence which makes it a potential target for intraperitoneal chemotherapy. Although the common way of administering chemotherapy is intravenous, nowadays, intraperitoneal administration of chemotherapy attracts a great deal of attention because of its counteraction effect on the natural spread of disease and because of the plasma-peritoneal barrier, wherein the peritoneum is poorly reached by traditional intravenous chemotherapy. The well-known concept of IP chemotherapy is to directly expose the tumor tissue to an extremely high concentration of antineoplastic agents by perfusing within the peritoneal cavity which could improve efficacy, particularly against microscopic residual disease and peritoneal carcinomatosis with an acceptable safety profile.[4]

Intraperitoneal chemotherapy has been long explored as an option for advanced-stage ovarian cancer and is routinely indicated for minimal residual diseases following primary debulking surgery. However, in a pharmacokinetics study, data suggested that IP chemotherapy would be effective also in patients with large-size residual disease, due to platinum-based therapy being absorbed via peritoneal capillaries that will reach the inner core of large tumors through the systemic circulation.[5]

To date, the strongest evidence for the benefits of intraperitoneal chemotherapy comes from GOG 172, a randomized phase III study of cisplatin administered intraperitoneally combined with both delivery of paclitaxel intraperitoneally and intravenously, published in 2006, which demonstrated a 16-month improvement in median overall survival over intravenous administration of the same drugs alone. This prompted the National Cancer Institute (NCI) to issue a rare clinical announcement at that time regarding the clinical use of IP cisplatin in the treatment of patients with minimal residual tumor,(<1 cm) in stage III EOC following an attempt at maximal cytoreductive surgery. [6]

Results of recent trials related to intraperitoneal

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Finalist, SGOP 2021 Interesting Paper Contest in Gynecologic Oncology, 17 November 2021 via Zoom webinar platform

Financial Disclosure:
The authors did not report any potential conflicts of interest.

chemotherapy (IP) demonstrated improvements in the survival of patients.[7] However, patients included in this trial had received upfront surgery and there was a scarcity of data that evaluated the efficacy of IP/IV chemotherapy following neoadjuvant chemotherapy and interval debulking surgery (NACT-IDS). In view of this limited data, this report aims to share our experience of intraperitoneal chemotherapy in a patient with clear cell carcinoma of the ovary who underwent adjuvant IP/IV chemotherapy following neoadjuvant chemotherapy and interval debulking surgery and is currently with no evidence of the disease.

Case Report

A case of 60 years old, G1P1 (1001), Filipino, married, who consulted due to bloatedness and gradual abdominal enlargement. The patient is known hypertensive with maintenance medications. Family history is non-contributory. She had her menarche at 12 years old with regular monthly cycles and had her menopause at 51 y/o. The patient is a non-smoker and non-alcoholic beverage drinker with no history of illicit drug use. She has no history of oral contraceptive use. Three months PTC she experienced bloatedness with accompanying gradual abdominal enlargement. There was no weight loss, bladder, nor bowel changes. She consulted a gynecologist and a whole abdominal ultrasound showed a large, complex mass predominantly cystic within the pelvic region measuring approximately 11.9 x 21.4 x 12.5 cm, and this mass exhibits septations and mural nodules with consideration of ovarian new growth. The patient was scheduled for upfront surgery. Intraoperatively, there was a huge cystic structure with a fluid-filled mass containing hemorrhagic fluid. The mass measured 25 x 18 x 12 cm, and densely adherent to the large bowel. The right ovary was normal however the uterus was not identified due to dense adhesions. The appendix was grossly normal. Optimal cytoreduction was not possible during this time hence they proceeded to do an exploratory laparotomy, peritoneal fluid cytology, adhesiolysis, and biopsy of left ovarian mass. The histopathology report of the left ovarian mass revealed clear cell carcinoma and the peritoneal fluid submitted was also positive for malignant cells. She was referred to our institution post-operatively for definitive management. Upon examination, the patient is ECOG 0, the abdomen is flabby with an abdominal girth of 92 cm with no fluid wave, with a pelvoabdominal mass measuring 12 x 18 cm on the left hemiabdomen crossing the midline which was fixed. On internal examination, the cervix measured 1 x 1 cm, smooth, with a fixed cul-de-sac mass measuring 6 cm in the widest dimension occupying the left fornix. The corpus and adnexa cannot be delineated due to the said pelvoabdominal mass. On rectovaginal examination, bilateral parametria were free. The whole abdominal CT scan showed a large complex abdominopelvic mass maybe ovarian in origin measuring 23.45 x 13.30 x 13.94 cm; predominantly cystic with solid components in its inferior aspect with no plane of resection. It exhibits internal septations with a slightly thickened wall in its left aspect. Anteriorly and to the right, the mass is seen intimately related to and causing displacement of the uterus. Inferiorly, it displaces the urinary bladder. There were no enlarged lymph nodes and bowels were unremarkable. Ca-125 was normal at 31.62 U/ml. The patient was staged as FIGO IIIC because of the presence of macroscopic peritoneal metastasis beyond the pelvis measuring more than >2 cm during the initial surgery.

Since the mass was non-resectable, the patient was given neoadjuvant chemotherapy with carboplatin AUC 6 + paclitaxel 175 mg/m^2 every 21 days. Reassessment was done every cycle of neoadjuvant chemotherapy. After the 3rd cycle, the pelvoabdominal mass had decreased in size measuring 10 x 10 cm with limited mobility. On internal examination, the cervix was 1 x 1 cm, smooth, the corpus and adnexa cannot be delineated due to pelvoabdominal mass. Bilateral parametria were free. The cul-de-sac mass measured 5 cm in its widest dimension and is still fixed. At this time the mass was still unresectable. Since there was a slow response to chemotherapy she was given additional two more cycles. On her 5th cycle of chemotherapy, there was an a markedly increase in the size of the pelvoabdominal mass which now measured 15 x 19 cm, solid, however movable at this time. On internal examination, the cervix was 1 x 1 cm, smooth, the corpus and adnexa cannot be delineated due to pelvoabdominal mass. Bilateral parametria were free. And the previously noted cul-de-sac mass was no longer appreciated. Interval imaging, confirmed the increase in size of the pelvoabdominal mass measuring 18.9 x 19.6 x 14.7 cm (previously 23.45 x 13.30 x 13.94 cm). Within the said mass shows no significant changed in the solid components in its inferior aspect. The urinary bladder is compressed inferiorly with intact soft tissue plane. Uterus is again displaced anteriorly and to the right with calcifications. The planes of resection are not clear in this scan. CA 125 was normal 29.43 U/ml. In view of this clinical findings wherein the mass seemed resectable, she was labeled to have stable disease and hence qualified to undergo interval debulking surgery. We proceeded to do IDS. On opening up, no ascites was noted. The surfaces of the abdominal and pelvic organs were smooth. There were no palpable pelvic and paraaortic lymph nodes. The left ovary was enlarged to 17 x 16 cm, cystic with solid areas. The small bowels were densely adherent to the supero-anterior surface of the left ovary. There were multiple adhesions of the small bowels to the anterior abdominal wall. The rectosigmoid colon was adherent to the posterior surface of the uterus and left ovary and the mass was inadvertently ruptured during adhesiolysis exuding 2000 cc of chocolate-like brown fluid. The right ovary measured 3.1 x 1.7 x 0.8 cm, and was grossly normal, on cut section, there were no solid areas, hemorrhages and necrosis. The corpus and cervix were grossly unremarkable as well as the fallopian tubes. The omentum was grossly normal. There were small bowel serosal tears 200 centimeters from the ligament of Treitz and 100 cm from the ileocecal valve and also serosal tears at the distal colon. There was no gross residual disease during this surgery. Exploratory laparotomy, adhesiolysis, total abdominal hysterectomy bilateral salpingo-oophorectomy, infracolic omentectomy, repair of the small bowel, and distal sigmoid colon serosal tear were done. Since there was no gross residual tumor, an intraperitoneal port was inserted. A small transverse incision was made in the midclavicular line, overlying the lower ribs, and a small pocket for the port was developed over the fascia covering the ribs. The catheter was inserted through a separate stab incision and tunneled under the subcutaneous tissue, just above the fascia, for at least 10 cm, until it reaches the port pocket, pulled into the peritoneal cavity, and flushed with heparin. The port was anchored with three permanent sutures to the fascia, to prevent rotation or migration.

The postoperative course was uneventful. The patient was discharged on the fifth postoperative day. The histopathological result confirmed the presence of ovarian clear cell carcinoma. The patient was started with IP/IV chemotherapy one month post operative and has been ascertained that the patient had no signs of perioperative complications. Chemotherapy was administered into the IP port using a 20 gauge right-angled needle (Huber needle). The treatment protocol comprised of IV paclitaxel 135 mg/m^2, diluted in 500 mL of saline for 3 hours on day 1, followed by carboplatin at a dose based on AUC = 6 administered through the IP port. For IP carboplatin diffusion, 1000 mL of saline was infused through the IP port during paclitaxel administration, and the calculated carboplatin dose was then administered in a bolus infusion. Paclitaxel (day 8, 60 mg/m^2, diluted in 1000 mL of saline) was administered to the peritoneal cavity for more than an hour followed by an additional 500 mL of saline. Chemotherapy was scheduled every 21 days. During infusion, the patient was placed in a semi-Fowler position with her head no higher than 30 degrees above the bed, both for comfort and to prevent dislocation of the needle. After the infusion, she was repositioned from side to side every 15 minutes for one hour to help disperse the infusate. After administration of chemotherapy, the port and catheter are flushed with at least 10 mL of heparin 100 units/ mL. The needle was then removed and the site occluded with a pressure dressing to prevent leakage of the infusate from the port. During the IP/IV chemotherapy, the index patient was regularly assessed for chemotherapy complications such as neurotoxicity, renal toxicity, myelosuppression as well as catheter-related problems such as signs of infection, catheter displacement and blockage, leakage, pain around the port pocket, abdominal pain and possible bowel perforation. The patient was able to receive 3 cycles of IV/IP chemotherapy with no untoward complications to the chemotherapy or to the intraperitoneal port catheter. The catheter was removed as soon as all of the courses of chemotherapy have been completed given the high rate of complications. Removal was done as an office procedure under local anesthesia. The incision was opened, the capsule of scar surrounding the port was cut with a scalpel, and the four sutures were identified, cut, and removed. The port and catheter were pulled out, without difficulty. A whole abdominal CT scan was done following her third cycle of IV/IP chemotherapy which showed unremarkable findings. Currently, there has been no signs of recurrence of the disease for 10 months as confirmed by imaging and clinical examination. The patient is advised to continue surveillance.

DISCUSSION

Standard therapy for patients with primary epithelial ovarian cancer deemed eligible for surgery is primary debulking surgery (PDS) with residual disease of less than 1 cm, followed by systemic chemotherapy with carboplatin and paclitaxel and this has been associated with a significant increase in overall survival (OS) and progression-free survival (PFS) as stated in the literature. However, for patients not medically fit for surgery, with poor performance status, or with a disease that is unlikely to be optimally cytoreduced, neoadjuvant chemotherapy (NACT) with interval debulking surgery (IDS) is an option. Our index patient was given neoadjuvant chemotherapy using carboplatin and paclitaxel since the attempted primary debulking surgery was not successful. While platinum plus taxane chemotherapy results in increased overall survival in patients with epithelial ovarian cancer, clear cell carcinoma is usually associated with poor response to chemotherapy and with high rates of recurrence than other types and has a poorer prognosis. Prior to the start of treatment, the patient and relatives were appraised that compared to the prognosis of serous carcinoma, that of clear cell carcinomas is poor, a factor attributed to their resistance to chemotherapy. Initially, we thought that the index patient is chemo resistant during neoadjuvant chemotherapy, however, despite the increase in the size of the mass which is evident in the interval imaging, surgery was considered after the fifth cycle since the mass was clinically resectable and the index patient was able to undergo IDS with no gross residual disease. In view of the intraoperative findings of no gross residual disease, the decision to insert an intraperitoneal port was made with this index patient. This is supported by the NCCN guidelines that recommend IP/IV chemotherapy for optimally debulked (residual tumor <1 cm) in FIGO stages II and III ovarian, fallopian tube, and primary peritoneal cancer[8]. However, most of the basis of this NCCN recommendation on intraperitoneal chemotherapy had a population who underwent upfront surgery and the index patient had interval debulking surgery following neoadjuvant chemotherapy (NACT-IDS) which is not a routine practice.

Given the limited studies on NACT-IDS followed by IP/IV chemotherapy, some trials explored the use of IP/IV in patients treated with the NACT approach. Both SWOG S0009 and OV21/ PETROC, have a unique approach to IP chemotherapy wherein they evaluated postoperative IP/IV chemotherapy in patients who underwent NACT followed by optimal cytoreduction by IDS.

The Southwestern Oncology Group conducted a phase II clinical trial examining 58 patients after IDS. Optimally debulked patients were given 6 cycles of IV/IP chemotherapy. Findings showed that outcomes were similar to those of previous trials of primary sub-optimally debulked patients.[9]

Like the SW00G9 trial, the OV21 is a randomized study on IV- versus IP-based chemotherapeutic regimens in women who received NACT following optimal IDS. Patients were randomized to receive an IV-based regimen versus an IP cisplatin- or IP carboplatin-based regimen. On Arm 1, patients received IV carboplatin (AUC 5/ 6) followed by IV paclitaxel 135 mg/m^2 on day 1 plus IV paclitaxel 60 mg/m^2 on day 8 every 21 days for 3 cycles to which the IP/IV protocol of our index patient was based. Both treatment arms were well tolerated, with no difference in the quality-of-life outcomes.[10]

In 2016, J. Mueller et.al evaluated the feasibility and outcomes of Intraperitoneal chemotherapy after interval debulking surgery for 128 patients with advanced-stage ovarian cancer and were given NACT. The authors found out that IP-based chemo after optimal IDS in advanced ovarian cancer is feasible and safe, survival outcomes are comparable between IV- and IP-based chemo after IDS, and complete gross resection at the time of IDS optimizes oncologic outcomes.[11]

Another recent study by Wang et.al on the effect of NACT-IDS with intraperitoneal chemotherapy after IDS showed that NACT with intraperitoneal chemotherapy after interval debulking surgery could improve the PFS of patients with advanced epithelial ovarian cancer compared to intravenous chemotherapy without significant differences in toxicity.[12]

Based on these results, the NCCN guidelines include both the cisplatin/paclitaxel IP/IV regimen and the carboplatin/paclitaxel IP/IV regimen as options for postoperative chemotherapy in patients who have NACT and IDS.

Historically, cisplatin was the most extensively and widely used agent for intraperitoneal chemotherapy. However, it is more toxic and more difficult to manage compared to carboplatin. Results of several studies have shown that the use of carboplatin as IP chemotherapy would be feasible,[13,14,15] hence we used carboplatin with this index patient.

Moreover, a recent open-label iPocc trial determined the efficacy of IP carboplatin compared with IV carboplatin in combination with IV paclitaxel in 655 patients with stage II to IV epithelial ovarian, fallopian tube, or primary peritoneal cancer, including those with bulky tumors. Results showed that Progression-free survival (PFS) is significantly longer with intraperitoneal (IP) over intravenous (IV) carboplatin, when combined with dose-dense paclitaxel, in patients regardless of residual tumor size after the initial surgery.[16]

Despite a proven survival benefit, clearly intraperitoneal/ intravenous chemotherapy has not been universally accepted for the treatment of EOC. Because of the catheter placement and regional delivery of the antineoplastic agent, IP/IV chemotherapy is associated with toxicity, including gastrointestinal toxicity, pain, infection, and catheter-related complications. These have been reported in the literature and supported in meta-analyses.[17] And fortunately, the index patient tolerated the neoadjuvant chemotherapy combined with IP chemotherapy using carboplatin combined with dose-dense paclitaxel with no toxicities nor catheter-related adverse effects noted. She was managed without having any delays in chemotherapy treatments. She is now on her 10th-month post IDS with no evidence of disease. Thus, even having a delayed response during the neoadjuvant treatment, the successful management of advanced stage clear cell ovarian carcinoma in this patient can be attributed to the neoadjuvant chemotherapy given in proper timing, having optimal cytoreduction during the IDS and the tolerability of the patient to IP/IV chemotherapy.

CONCLUSION

Selecting an optimal, evidence-based treatment strategy after IDS in a clear cell ovarian carcinoma is of crucial importance since the surgical decision-making and chemotherapy administration choices can potentially affect survival. Due to the fact that most often these are chemo-resistant tumors, cytoreductive surgery to no residual disease remains the best therapeutic approach in order to obtain improved long-term survival. Informed selection of the best treatment for any patient is recommended. IP/IV chemotherapy is a complex and challenging procedure but randomized phase III trial and meta-analysis support its benefit in the treatment of select groups of women with epithelial ovarian cancer however, currently, we have not arrived at the optimal intraperitoneal/ intravenous chemotherapy regimen, which balances efficacy with toxicity and quality of life. Awareness about the complications is important to decrease its occurrence to achieve easier completion rates of IP/IV chemotherapy to increase adaptation of this approach in clinical practice. Finally, effective and safe delivery of intraperitoneal/intravenous chemotherapy requires the expertise of a skilled team. ■

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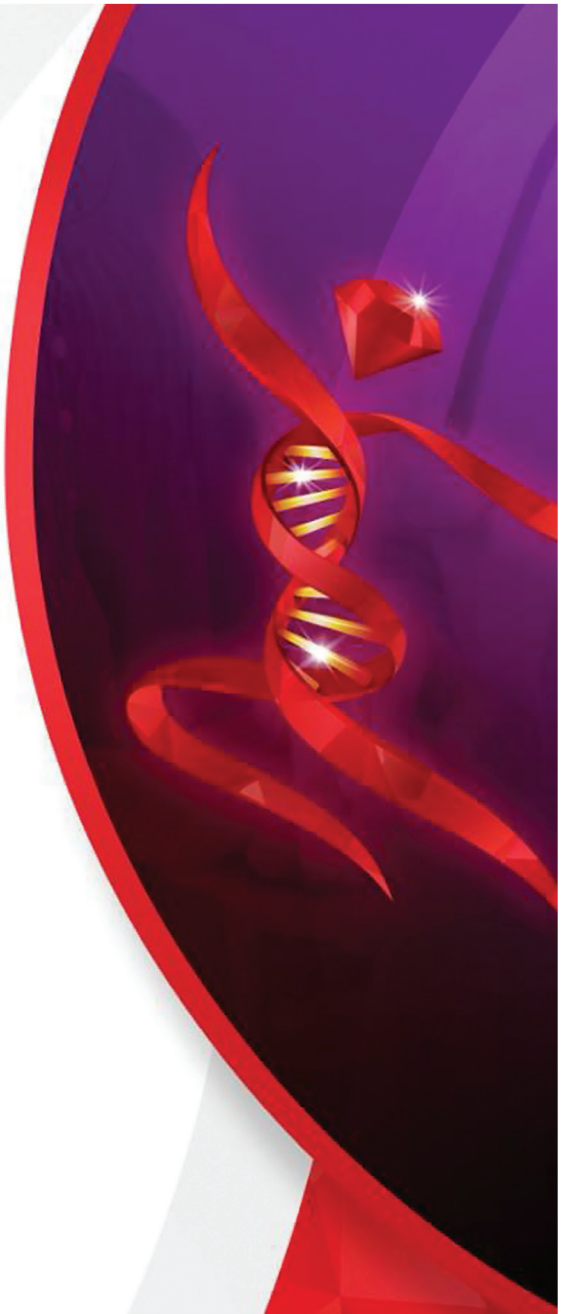

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